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U.S. Health Effects Research Lab., Research Triangle Park, N.C.

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The report is a proceedings of a symposium convened at Chapel Hill, North Carolina, October 26-28, 1977. Five major topics pertaining to the use of humans as experimental subjects are addressed in this volume: philosophy of clinical research, environmental and physical safety considerations in human exposure facilities, the EPA human studies programs, and special considerations and approaches in environmental clinical research. The first four parts consist of twelve formal papers covering issues such as ethical and legal considerations surrounding the use of human subjects, environmental controls and safeguards, and electrical surveillance and integrity. Following each paper is a summary of the discussion that took place after the paper was presented to the symposium participants. Part five is a panel discussion composed of four brief presentations and an exchange of comments among panel participants.

The purpose of these proceedings is to help identify, through open discussion, the problems connected with using human subjects in clinical research.

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Methodologies and Protocols in Clinical Research: Evaluating Environmental Effects in Man

Symposium Proceedings

May 1978

United States Environmental Protection Agency
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Preface

The relative affluence of the industrial age has been attained at the cost of degrading the quality of some aspects of life. Conditions of the sort described by Dickens have, in large measure, been corrected. But there remains the pervasive and insidious danger of man's increasing ability to alter his environment. In the final analysis, mankind is concerned with the repercussions of environmental changes on his health and happiness. Both of these qualities are very difficult to measure in a quantitative way. This symposium, however, addresses some aspects of the quantitative assessment of health status.

In some respects, the proper study of environmental influence on human health is the study of humans whose environment is altered in a controlled way. The methodologic, ethical, legal, and social aspects of such research are the major topics of this symposium. Because of the inherent problems and restrictions in these major topics, there are many environmental health questions that will always remain beyond the purview of clinical research. Because of the unique advantages of clinical research, there are some environmental health questions that are answered best by clinical research. One of the objectives of this symposium is to formulate criteria for identifying which kinds of environmental health questions are particularly suited to the clinical research approach and which definitely are not.

The levels of sophistication involved in most aspects of clinical environmental research is increasing rapidly. Those who are relatively new to this field may assume that space age technology reflects the recent advent of this kind of research. This is not true. Modern clinical environmental research draws on a rich heritage of simple, elegant studies that have provided the foundation of human stress physiology. I hope we are successful in using the tools of modern technology in responding to the needs of modern society. To accomplish this, we must continue to perform well in the tradition of those whose work has made ours possible so that we can improve the quality of life for those who follow us on this planet.

John H. Knelson, M.D.
Clinical Studdies Division

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PHILOSOPHY OF CLINICAL RESEARCH

Moderator: Milan Hazucha, M.D.

Ethical Considerations in Research Involving Human Subjects

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There is, I dare to think, broader consensus among physicians and ethicists on the meaning of "clinical research" than on "ethical issues," so I want to introduce these observations on ethical issues in clinical research by commenting on what constitutes an ethical issue. No doubt, you have noticed that the words "ethics" and "morals" are heir to many interpretations; indeed, they are frequently employed as synonyms in medical literature. Therefore, my initial focus will be to discriminate between these terms.

ETHICS AND MORALS

In the history of Western philosophical and theological reflection, ethics (or moral philosophy) is typically characterized by a spirit of radical inquiry; it does not attempt to supply solutions for moral dilemmas, but it does undertake to provide a rational framework for comprehending the complexities of moral judgment. Put simply, the moral question is a "what" question—what ought I do, what good should I seek, what is the right action in this situation, what end should I pursue? Correspondingly, the ethical question is a "why" question—why should I do this, why do I seek this good action rather than some other action, why is this action right or appropriate?

In other words, ethical questions attempt to reference action

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to an affirmative warrant, they ask whether there is a proper reason for making a particular choice, and whether there is coherence and congruency between what one believes and how one behaves. On these terms, a moral action is one that expresses an antecedent value commitment.

In this classic study of American racism, Gunnar Myrdal argues that the roots of American racism lie in a contradiction between American political and social ideology. In his book, An American Dilemma, Myrdal shows that racism is the product of a distancing, a gap, a discontinuity between the "American creed" and the "American deed." The "creed" declares that all persons are created equal; the "deed" treats some persons as superior and others as inferior. The Biblical word for this disparity is hypocrisy (from the Greek hypokrisis, literally, to act a part, to pretend to be what one is not), and immorality is the name we give to conduct that is contradictory of, or in conflict with, character. Thus, one useful reason for distinguishing ethics from morals is to undertake a rational analysis of the value predicates of actions and to test their expression in behavior.

DESCRIPTIVE/PRESCRIPTIVE ANALYSIS

The analysis of the value predicates of action and their expression in behavior is principally of two sorts: descriptive and prescriptive, or operational and normative. In descriptive analysis, the values that appear to be informing action are inferred from the actual conduct of individuals or groups. Thus, if a person or group steals, it is not unreasonable to suppose that (at least in those situations in which stealing is practiced) there are no absolute property rights. It would appear further that property (at least the property in this situation) appropriately belongs to whoever can possess it, by fair means or foul. Conversely, if a person or group does not steal, it is reasonable to suppose that the mores of this group prohibit it and, moreover, that property is somehow thought to be inviolate. Descriptive analysis identifies the ethics of persons or groups inductively from observation of actual conduct.

On the other hand, prescriptive or normative analysis takes its cue from an articulated system of values—usually a formal statement that affirms what is true, beautiful, and good—to ask two kinds of questions: (1) In view of a given statement of what is valuable, what actions are derivatively appropriate? If this statement represents what we believe, how ought we to behave? (2) Given a statement of what is valuable, are the actions we observe appropriate? Are these modes of conduct coherent with this character, are these actions congruent with these affirmations?

I tell my classes about the case of an avowed and apparently devout cannibal who is a practicing vegetarian! Descriptive analysis says simply that this is an immoral person—he does not practice what he preaches, there is no congruency or coherence between what he affirms and how he acts. Prescriptive analysis, on the other hand, is more concerned with the predicates of the cannibal's behavior; that is, whether cannibalism qua cannibalism is an appropriate or right or good philosophy. Depending on the answer to this question, prescriptive analysis will tend to make one of two judgments—either that cannibalism is a licit philosophy, in which case, this "vegetarian cannibal" is confused or cannot be responsible to his conviction and therefore is not a dependable moral agent; or that cannibalism is an illicit philosophy, and while this person may be doing the right thing, he's doing it for the wrong reason. In either case, a negative judgment is rendered in the absence of clarity and continuity between creed and deed.

ETHICAL ISSUES AS MORAL DILEMMAS

To speak about ethical issues in clinical research is to engage this same genre of questions and judgments. But in this context, our attention is drawn to physicians (and possibly others) who (a) are simultaneously acting under the governance of both personal and professional ethical sensibilities, which suggests that conflict may sometimes occur between these two, and who (b) are carrying out scientific investigations on patients who have presented themselves for care and treatment, which also suggests that a disturbance may be experienced, this time by patients who learn that they are experimental subjects. In addition, physicians may find it difficult to reconcile their responsibilities as clinicians with their responsibilities as investigators.

So, an "ethical issue" can be either or both of two sorts: it can be identified as an incongruence or discontinuity between affirmation and actions, or it can be identified as an inappropriate affirmation or a mistaken value system. In both instances, an "ethical issue" ordinarily presents as a moral dilemma.

In today's society, the ethical issues in clinical research seem to be basically of the first sort, that is, as a tension or distancing between belief and behavior. As one reads the literature of clinical investigations—say, from Nuremberg to the present—it is evident that the principal ethical questions ask what research is appropriate under already established guidelines, and whether investigators are, in fact, honoring those principles in both protocol and practice. Of course, innovations in therapy together with curiosity generated out of previous studies constantly push against the boundaries of those principles, and occasionally, there is talk about reformulating the goals and goods to which medicine is committed.

It has been suggested, for example, that cloning and cyborg-androids offer the prospect of larger and less restricted pools for "human" experimentation, and that we should move ahead with technologies in anticipation of the benefits that would result from their use. To cite only one instance: The care with which the current National Commission for the Protection of Human Subjects has proposed and promulgated guidelines for studies using abortuses, prisoners, the mentally infirm, and others as potential research subjects makes it fair to say, I think, that there is a formal consensus in the U.S. concerning the values and obligations of clinical investigations. The ethical standards for clinical investigations appear to be settled if one takes these documents to be normative statements.

THE ETHICS OF INVESTIGATION

What are the standard values and obligations of the medical profession that govern clinical investigations? Their documentary expression can be found (among other places) in the Nuremberg Code,[3] in the Declaration of Helsinki,[4] in the policies of DHEW regarding the protection of human subjects,[5] and in the AMA's "Ethical Guidelines for Clinical Investigation."[6] A careful reading and content analysis of these statements shows that their substantial points focus on two principal interests: the study and the subject. Moreover, three constituent heads can be denominated under each of these two governing titles: the sections that comment on the nature of the study typically address its purpose, its design and conduct, and its results; and the sections that speak to the role of participants in the study accentuate the physician-patient relationship, consent, and risk. All of these sections together constitute, in this literature, the ethical issues appropriate to clinical investigations, at least as perceived by those who formulated these statements.

Study Guidelines

The purpose of clinical studies, according to the Nuremberg Code, "should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature." In Helsinki, the World Medical Association declared that, "It is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity." The AMA guidelines for clinical investigation, adopted in 1966, endorse these same ethical principles. In sum, they seem to state that what initially legitimates clinical research is the need to test experimental hypotheses on human subjects to extend scientific knowledge and to alleviate human suffering.

In addition, this purpose must be acknowledged in the design and conduct of the study. "A physician may participate in clinical investigation," according to the AMA guidelines, "only to the extent that his activities are a part of a systematic program competently designed, under accepted standards of scientific research, to produce data which is scientifically valid and significant." Moreover, both the Nuremberg and Helsinki statements insist that the research should be designed and based on animal experiments and the natural history of the disease, and conducted only by scientifically qualified persons from whom "the highest degree of skill and care should be required." The point of these admonitions is that a study must be ethical in its design and conduct if it intends to be ethical at all; that is, rather than judge the ethical aspects of a study solely on a post hoc basis, there are possibilities for ethical evaluation already present in a study's intention and methodology.

Finally, these ethical guidelines hold that the results of the study should coinhere with its purpose. If the goal of clinical research is to test experimental hypotheses on human subjects to extend scientific knowledge and alleviate human suffering, the results of the investigation ought to show this. Sometimes constructive advances in knowledge and innovative therapies are achieved, and sometimes it is discovered that the positive accomplishment of a trial is to show that a given hypothesis is incorrect. In either case, the ethical burden is placed upon the investigator to show that the results of the study are in keeping with its purpose.

The Subject's Rights

The second principal interest that these documents address concerns the participants in clinical research and the two kinds of special consideration due them. Presuppositional to concerns for consent and risk is the physician-patient relationship. Without this, and without its being conceived in a certain way, there would be little or no point in going on to talk about consents and risks. The AMA guidelines state unambiguously that the investigator "should demonstrate the same concern and caution for the welfare, safety and comfort" of the experimental subject "as is required of a physician who is furnishing medical care to a patient independently of any clinical investigations." The Declaration of Helsinki is, if anything, more rigorous: "The doctor can combine clinical research with professional care. . .only to the extent that clinical research is justified by its therapeutic value for the patient" because "it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out."

These notions of subjects' rights and physicians' duties are reinforced in both the Nuremberg and Helsinki documents, with provisions for investigators to terminate, and subjects to withdraw from, experiments at any stage. What appears to be clearly at stake, and what is clearly affirmed in all these documents, is a sensitive and generous humanitarianism that imposes equally upon the investigator and the subject. Neither can treat or regard the other as merely a means to an end, because there is a fiduciary relationship between them, which is an inviolable end and which transcends the immediacy of any enterprise in which they may be jointly engaged.

In this context, concerns for consent-getting and risk-assessment make sense as logical extensions of the primary commitment to humanitarian ideals. Thus, the Nuremberg Code states that "voluntary consent of the human subject is absolutely essential," and the Declaration of Helsinki asserts categorically that "clinical research on a human being cannot be undertaken without his free consent, after he has been fully informed."

Each of us could probably cite too many examples of the failure to honor this fiduciary relationship. I recently experienced an especially poignant demonstration of this. I was on an airplane, comfortably settled into an aisle seat and reading an issue of The Lancet when, almost immediately after we were airborne, a woman who was sitting across the aisle leaned toward me and asked, "Are you a doctor?" "Yes," I said, "but probably not the kind you mean." "Then what kind of doctor are you?" she inquired. "A Ph.D., a doctor of philosophy." "Well," she said, "maybe you can help me anyhow." And then she proceeded to tell me her story.

In early childhood her husband had received a diagnosis of "cerebral palsy"; in manhood he had experienced grand mal seizures; and now, more recently, he had undergone episodes of uncontrollable violent behavior during which he had hurt both himself and his wife. She was now returning home after having admitted her husband to a university medical center under the care of a neurosurgeon to whom she had been referred. She had seen this doctor, but their meeting had been very brief.

Thereafter, she was contacted by one of the neurosurgeon's residents, and it was with him that she had a conversation about her husband's situation. She did not learn very much from that conference because, she said, "He talked funny and I couldn't understand him." In response to my questions, it developed that the resident also had "different eyes." We concluded that he was probably not a native American. In any event, this woman did not understand what she was told by the resident. She had no opinion about faulting the young doctor for failing to communicate with her, and she turned aside my question about the neurosurgeon's responsibility to discuss her husband's case by saying that "he is so busy...he is very important and works very hard...lots of people like my husband depend on him...he's just too busy."

This woman is a registered pharmacist, and I would have guessed her to be in her early thirties. She had signed the admissions forms and her plans were to return to the hospital in ten days, when her husband's initial work-up and perhaps other preliminary or exploratory procedures would be completed, to be present at the time of his surgery. She planned to return to the medical center in the early morning of the day when surgery was scheduled for noon; she did not know anything about any consent forms, but did know that she would be expected to sign some papers when she went back to the hospital.

She could not describe what was going to be done to her husband over the next ten days, nor did she know what surgical procedure was scheduled at the end of that period. When I inquired whether her husband's treatments, whatever they were, would be directed to his cerebral palsy or his epilepsy, the wife's response was, "No, it's for his violence." "Well," I asked, "what surgery is going to be done?" "I don't know," she said, "but that's what I wanted to ask you about. I saw something about 'thalamus' and something about 'frontal.' Do you know what those mean?" I avoided answering that question, and asked whether she was satisfied with what she knew about her husband's treatment, and whether her questions to me indicated that she needed to know considerably more than she did. She acknowledged the force of both those questions, then added, I thought somewhat plaintively, "But they wouldn't hurt him, would they?"

This was an uncomfortable conversation for me—uncomfortable for all the conventional reasons, to be sure; but more than that, it was uncomfortable because I am familiar with the symptoms she described and some aspects of the "innovative therapy" of "psychiatric neurosurgery" being undertaken in that medical center for the control of violence. I did not want to alarm this woman, not only because I am not a medical doctor, but also because I did not have all the relevant facts before me. Nevertheless, I was disturbed by what I suspected was likely to happen to her husband, and my uneasiness was escalated by the knowledge that this woman and her husband lacked the most rudimentary information and understanding of the husband's treatment. Without the necessary information and understanding, they could not participate significantly in the decision-making process. Preconditional to that, it was plain that the presumption of a convenantal bond, a fiduciary relationship between patient and physician, had been violated.

By now the airplane was beginning its descent, and I wanted to let her know, without adding to her anxiety, that I thought the way her husband's case was being handled was very inappropriate and unsatisfactory. I suggested that she contact a local neuosurgeon, explain the situation, ask him to contact the medical center neurosurgeon on her behalf, and then have him explain to her her husband's treatment. I also suggested that she make arrangements to talk with the attending surgeon prior to surgery and before signing any further forms. Even with these suggestions, I felt frustrated and powerless. As she left the airplane, she expressed her disappointment that I would not or could not say any more than I had about what was likely to be in store for her husband.

THE PATIENT'S CONSENT—AN ETHICAL ISSUE OF THE 20TH CENTURY

I find it interesting that, while the moral traditions of Western medicine contain provisions for a consent mechanism, the prominent role of consent as an explicit issue in medical ethics is a relatively recent one. In fact, there is no mention of consent in the Hippocratic Oath, or by Maimonides in the 12th century, or by other pre-19th century medical authorities. Indeed, there is no apparent concern among classical authorities for a special ethical obligation with respect to consent—and this is the case for both experimental and established therapies.

The most persuasive explanation for this state of affairs is two-fold: (1) The beginning of human experimentation is typically identified with William Harvey's research in human circulation in the early 17th century (1628); however, the great commitments to research as a predominating direction of scientific medicine were not expressed until the mid-20th century. So, while there has always been curiosity in the clinical setting, it has only been in relatively recent times that clinical investigation has achieved such high priority and institutionalization. (2) Concurrently with this phenomenon of the socialization and politicization of medicine, an intellectual attitude developed in Western culture, which had as its primary objective the yielding of information through systematically designed experiments. This attitude, in turn, provoked conflict and competition with an older principle of primary patient benefit from medical intervention.

World War II, and the Nazi medical experiments in particular, exposed the weakness of experimental ethics that were based either solely or largely on social utility or scientific advance; and Nuremberg, although it focuses chiefly on experimentation, has become the landmark in the evolution of consent as a prominent issue in the ethics of health care. (I want to add, parenthetically, that the force of the Nuremberg Code is unquestionably directed toward the protection of patients and subjects, although it was propounded to guide physicians in carrying out studies on human subjects. In recent years, however, and in the wake of wide exposure of unethical studies and malpractice litigation, we are observing a subtle shift in the intention of consent-mechanisms from patient-subject protection to physician-investigator protection.)

Since Nuremberg, four types of consent situations have been plainly identified: (1) the therapeutic setting, in which treatment is specifically and exclusively directed to the benefit of the primary patient (e.g., appendectomy); (2) yet another therapeutic setting, but one in which the benefit of treatment is specifically and exclusively directed toward another recipient (e.g., tissue and/or organ transplantation involving a living donor); (3) the experimental setting, in which general or specific information is sought by procedures that are unrelated to a primary patient's (or subject's) care, but which may benefit others and/or increase medical knowledge (e.g., mass screenings for hypertension or transmission of hepatitis); and finally, (4) permutations or combinations of the preceding situations, in which a treatment of unknown efficacy and safety is administered both for possible benefit to patients (or subjects) and for potential extension of medical information (e.g., new chemotherapeutic agents for carcinoma).

In all of these settings, the implementation of adequate consent-getting has been left primarily to physicians. Indeed, the Nuremberg Code states explicitly that consent procurement "rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated with impunity." The literal meaning of that last phrase, "with impunity," is "with freedom from punishment or penalty." It is my experience, by and large, that consent-getting is nevertheless regularly delegated to either nurses or house officers. This practice presents the kind of ethical issue, which in my judgment, is our foremost concern—a mode of behavior that contradicts the stated ethical principle.

The consent process is complex enough in itself without this kind of obviously faulty procedure that could be easily remedied. Since Nuremberg, it has been generally acknowledged that a valid consent rests upon and consists of three elements: information, freedom, and competency. Thus, a consent is valid if it is secured from a patient or subject who is knowledgeable, who agrees voluntarily, and who is compos mentis (or who, in the case of legal or mental incompetency, is represented by a guardian). In this context, I would like to plead for abolition of the phrase, "informed consent," because it misrepresents (both intentionally and grammatically) what is required in a valid consent.

But even if this misanthropic phrase should disappear from the medical lexicon, consents will remain problematic because it is difficult (perhaps, in an absolute sense, impossible) to assess precisely and accurately the extent to which any given patient or subject is informed, free, and competent in the consent situation. I have not found any consent situation (except, perhaps, for a genuinely elective procedure) which unambiguously satisfies pro forma the full range of interests signified by these elements. Moreover, I do not know of any single rule or protocol which in itself is comprehensive enough to guard all the contingencies and to guarantee adequacy.

I do not, however, conclude that we should abandon the concept of valid consent or blunt our moral sensibilities sufficiently to enable us to accept a more imperfect model. Rather—and presuming the subject's competency, which among the three elements of valid consent is customarily the easiest to certify—I believe that it ought to remain the physician's personal and professional struggle to fulfill the criteria for valid consent, by heightened sensitivity to all the elements that comprise voluntary consent, and by strenuous efforts toward full and complete disclosure of information to the patient's understanding.

Ideally, the consent situation is a covenant between persons, a fiduciary relationship, which is intended to guard and protect while simultaneously opening to larger possibility the common humanity of the parties to a shared goal. That way of viewing the consent situation is easily forgotten or neglected in the day-to-day routinization of research, or in the enthusiasm for a study. But acknowledgement of the consent situation as a fiduciary relationship, by both physicians and patients alike, will probably go farther than any formal requirement toward respecting both the spirit and the letter of the consent requirement.

RISK-ASSESSMENT

The Nuremberg Code asserts that "the degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment," and the Declaration of Helsinki similarly expresses its formal interest in risk-assessment by stating in its "Basic Principles" that "clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."

However, none of the documents venture to define precisely what constitutes an ordinate or inordinate risk, although the Nuremberg statement does provide that "proper preparation should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death." This commentary is not insignificant. Unlike the FDA requirement, which states only that drugs must be "safe" and "effective," but does not further explain or define these categories, the Nuremberg statement offers some clues about which conditions constitute inordinate risk.

Diagnostic precision must be developed in the applicability of clinical studies, just as there is need for technical and scientific excellence in research design. Those human trials that have treated indiscriminately the application of an innovative therapy have tended to be the most disastrous. For example, the use of a special high protein diet in the treatment of liver disease seemed to have a sound theoretical basis and to be administratively innocuous, but in the absence of the demonstrated benefit of this regimen, a decade passed before it became apparent that many patients were dying in hepatic coma as a result of this diet. That kind of risk appears to be inherent in any experimental study, but my point in citing this instance is to show that the risk need not be made inordinate by accepting a study as a success before adequate evidence is in to prove its validity.

Withal, three things seem clear: (1) the risk factor will vary from study to study, depending on the nature of the disease, the condition of the patient-subject, and on other factors that are relatively unique to the situation; (2) the physician's initial obligation—primum non nocere—is his minimal duty toward subjects, and their protection "against even remote possibilities of injury, disability, or death" is an appropriate extension of that basic desideratum; and (3) a good research design will identify both potential and/or anticipated risks and make provisions for unpredictable and unexpected risks.

While these aspects of the ethics of human experimentation deserve careful consideration in every study that involves human subjects, they impact with special emphasis on research in the clinical setting. Anyone with experience in both kinds of investigations, i.e., when combined with professional care and when conducted in a non-therapeutic setting, knows that the personal and interpersonal dynamics of these two settings can be, and usually are, remarkably different. For example, there is a heightened vulnerability among subjects who are also patients. This calls for uncommon sensitivity on the part of primary care physicians who are also, in these cases, clinical investigators.

ETHICAL AND MORAL DILEMMAS IN THE RESEARCH SETTING

There are ethical issues in clinical research that, like the poor, seem destined to be with us always. This is so largely because it is the task of ethics to probe behind the "what" and the "why," and to reference action to an affirmative warrant by establishing the truth and value claims of that warrant. So long as research behaviors probe and push against settled ethical boundaries, so long will it be incumbent upon us to reexamine and reassess our moral predicates. I know, of course, that remarkable and gigantic strides have been made in scientific and technical achievement, and that most if not all of these achievements owe their genesis to research and experimentation. But I also know that the ethical dilemmas of society are not rooted there, and that the moral crises that confront us do not emerge from the risks that attend our scientific accomplishment or the perils that accompany the promise of our technological triumphs.

Our ethical dilemma is actually a set of questions: Can we agree upon a common set of values? Is there a firm consensus among us as to what is true and good and beautiful? Can we assume that we share common notions of duties and rights? And our moral dilemma, correspondingly, interrogates our conduct: If we can agree upon the principles of virtue, can we then be clear and unconfused about the practice of virtue? I ventured to observe at the beginning that the ethical issues that confront us today are derived principally from incongruence or discontinuity between formally adopted professional affirmations and the embodiment of these ideals in the research setting. If that is so, our ethical predicament represents something of an inversion of the experimental hypothesis; in this instance our problem is not that "we need to know more in order to do better" but that "we don't do as well as we know."

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Discussion Summary

Conference participants raised three principal questions following the presentation of Dr. Smith's paper.

First, who should an investigator consult (besides himself) to assess accurately the degree of risk and the scientific merit of a research proposal? It was suggested that there is no set formula to determine what the risks of a particular study might be to the research subject.

In essence, it is the principal investigator who must assume responsibility for selecting the appropriate panel to assess a proposed study's risks. The principal investigator himself is certainly among those to assess the study's more scientific or technical risks, in addition to its scientific merit; but other experts also typically are invited to assess both the degree of risk and the importance of the study.

The second question dealt with the subject's motivation to participate in a study. Historically, one of the most important thrusts in clinical research has been that the benefit of research accrues to the subject. Today, the research subject is frequently less able to benefit directly from the research in which he is involved. Thus, whatever benefit the research subject gains is via his membership in society. Given these factors, what motivates an individual to become a research subject?

In large-scale studies, the question of personal benefit usually is not raised between the research subject and the investigator. Rather, the questions that are typically discussed deal with the issue of personal safety and whether certain people ought to be allowed to participate in certain studies. Thus, the consent mechanism looms large.

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For example, on the one hand, consent forms should protect subjects from poorly designed, unsafe experiments. And on the other hand, consent forms should ensure that the subject is well aware of his or her involvement in the study. Thus, from one subject's perspective, the emphasis tends to be on protecting the study subject, rather than on assessing the personal benefits to be gained from participating in a research study.

A final question focused on the dividing line between social utility as a justification for clinical research, and the subject's rights to protection and safety. Discussants agreed that there is no formal prescription with which to determine where this imaginary dividing line lies. It was noted, though, that some countries emphasize the social benefit to be gained from research using human subjects over the individual's rights.

Legal Aspects of Using Human Subjects in Environmental Research

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In this presentation, I will discuss the principles of law that govern liability of one person to another when something goes wrong, as those principles might apply to persons using human subjects for environmental research. At the outset, I must tell you that there is no series of legal rules, no "do's and don'ts" for you to take note of and follow so that you can live happily and judgment-free ever after. The legislatures of the state and federal governments have not addressed themselves to your legal problems concerned with using human subjects in environmental research, nor have the appellate courts, as far as I know. Your problems, to use a hackneyed phrase, aren't exactly a household word. They are not problems that have excited the press or the public. The result of this absence of pre-established legal rules and guidelines means that you are on a frontier of the law. Like the pioneers who pushed westward beyond the reach of the settled communities with settled laws, your scientific endeavors have likewise moved you into an area where the law has not yet reached. So, I have this warning for those who came with pencils poised to record a series of rules which, if followed, will enable you to pursue your research free of significant legal concerns: You are about to be disappointed! Instead, my message to you is this: As regards the legal implications of your activities, you are going to have to adjust to the fact that you will be living with a great deal of uncertainty for many years to come.

When I say the law is uncertain, I don't mean it is nonexistent. It is not as though you are out in trackless, weightless space, starting from scratch. The past, it is said, is the prologue to the future. The frontier communities were guided by the laws and the rules of the communities they left behind when they drew up the new laws and rules that would shape their future. So, we too can get some understanding of the legal problems that lie before you by examining the development of the law in areas that are related to your own legal concerns. What I propose to do is review some developments of the law in areas that the courts and legislatures would be likely to look to for guidance. In doing so, I hope I can help you to understand how and why you, as scientists, may become involved with the law and with lawyers.

A RESEARCH SUBJECT IS INJURED—WHO'S RESPONSIBLE?

Let's assume a hypothetical situation as the framework from which to discuss your legal rights and responsibilities in the event that a human subject of your research suffers injuries during the course of, or as a result of your experimentation. A man in his late thirties volunteers to be a subject in your research program. The man is interviewed carefully by your staff. He is told that he will be exposed to sulfur oxide gases in the air he breathes, and that he will be asked to perform certain physical activities, during which certain bodily functions will be electrically monitored. The volunteer is told that the combination of sulfur oxides that he will be exposed to is 10 percent higher than the amount normally present in the ambient air in a highly polluted urban area, say, Gary, Indiana.

The volunteer is told that the effect of this amount of gas in the air on humans has not been studied, and, as a result, the effect on the volunteer cannot be predicted. The volunteer is told that he is taking a risk for the benefit of scientific research. He indicates that he understands, and is willing to do so. The volunteer agrees to accept $4.50 per hour for a 48-hour period, during which he will be exposed continuously to controlled amounts of sulfur oxides. When the experiment has been under way for about 36 hours, the volunteer becomes violently ill and collapses.

We've said that there is little law to tell us who is responsible for what in this precise situation. But what lessons are taught by our historical review of the law in related fields? The first lesson is one that you don't have to be a lawyer to understand and that is, the law is a great Monday morning quarterback. The absence of definitive legal guidelines does not prevent the law from second-guessing your judgments. In fact, hindsight is one of the mainstays upon which the law is based. So, lesson number one is: "The absence of an existing legal standard does not prevent you from being judged against a standard that has developed after the fact." A second general lesson is that, even if there were some court decisions relating to your case, they would not remove the uncertainty as to the legal consequences arising from a specific situation. Generalization is difficult because the rights and responsibilities depend so much on the peculiar facts of each case. Furthermore, different courts may decide the same issue in opposite ways.

For example, in 1950, the New York Court of Appeals (which is what New York calls its Supreme Court) held that the manufacturer of an onion-topping machine was not liable to a worker whose fingers were cut off when his hands caught on the machine's revolving steel rollers. Although the injury could have been prevented by an inexpensive guard or a shut-off device within the operator's reach, the Court ruled for the manufacturer and against the worker, because the hazard was obvious. The Court said that the manufacturer had no duty to protect the worker from obvious hazards.[1] However, in 1966, an Illinois Appellate Court held that a manufacturer was liable for injuries caused when the operator's hand and arm were drawn into the unguarded rollers of a corn-picking machine. The Court said that the design of the machine, without guards against obvious hazards, was "unreasonably dangerous."[2]

In 1970, the California Supreme Court held a manufacturer of an earth-moving machine liable for the death of a worker who was run down by the machine because the machine's engine box prevented the machine operator from seeing clearly, despite the fact that the "blind spot" was obvious to the machine owner.[3] I suspect that if the New York Court were now to decide the onion-topping case, its decision would be in line with the decisions of the cases in California and Illinois. So, lesson number two is: "Court decisions won't necessarily remove the legal uncertainty that surrounds your actions."

THE LEGAL BASIS FOR LIABILITY

I want to discuss some of the specific problems created in our hypothetical situation, but before I do, I have another disclaimer. I am going to talk about substantive issues, not the procedural issues lawyers often raise to prevent the real issues from ever getting decided. For example, I am not going to discuss the statutes of limitations, which enable a court to avoid deciding the substantive issues because the lawsuit wasn't filed soon enough. Nor will I discuss sovereign immunity—the rule that prevents some governments from being sued without their consent.

Returning to our hypothetical example, let's assume that the equipment functioned perfectly, but the operator carelessly allowed too high a concentration of sulfur dioxide to build up, or that he failed to observe warning signals, or otherwise "goofed," and that the operator's negligence caused the volunteer's injury. Under those assumed facts, the operator's employer and the operator are liable to the volunteer. Liability is based on the concept, as old as American jurisprudence, that a person is responsible for his mistakes that cause injury to others, if he knew, or should have known, that others might be injured. This is the so-called "fault concept" which, although under fire, is strongly entrenched in American law.

Now, let's assume that the operator was alert and following instructions but because of inadequate instruction, he did not know that the readings on the monitors measuring the volunteer's vital signs had exceeded safe limits. Under the fault concept, the laboratory would probably be liable. The laboratory was negligent in failing to properly instruct the operator. So, under the fault concept, before the laboratory can be liable, the laboratory, or its employee, must have been negligent, and the negligence had to be a substantial contributing factor to the injury suffered.

However, the fault concept is not the only basis for the laboratory's liability. Another basis for liability is the concept that is often called "strict liability" or "liability without fault." Let's assume that the volunteer was injured because a monitoring device which would have warned the operator to reduce the supply of sulfur oxide gases did not operate properly. Assume, for discussion, that there was no way that the laboratory could have known about the defect in the monitoring device. In this case, the laboratory is probably liable to the volunteer, even though the laboratory is totally without fault. The basis for liability is public policy.

LIABILITY AS THE CONSUMER'S SAFEGUARD

In the last two decades, the courts, with the acquiescence of state legislatures, have been attempting to protect individuals from physical injuries caused by the ever-increasing number of complex gadgets in our technological society. The rules of strict liability, or liability without fault, were developed to protect consumers from goods that have a defect that could cause injury. But these rules have been expanded rapidly into other situations. For example, in most states, it is now law that a person who sells a defective product that is unreasonably dangerous to the consumer is liable for physical harm caused to the ultimate user, even though the seller exercises all possible care in the manufacture and sale of the product.[4] I strongly suspect that these principles of law will be applied as well to determine the liability of an environmental research laboratory to its volunteer human subjects.

The trend of the law has been to extend the rules of strict liability to allow recovery by persons who are not consumers or users of a product, and also to hold liable persons who are not the manufacturers or sellers of a product. The California Supreme Court allowed a person who was injured in a head-on collision with another car, to recover from the manufacturer of the other car whose defect caused the accident.[5] Similarly, the Michigan Supreme Court allowed a bystander injured by an exploding shotgun shell to recover from the ammunition manufacturer.[6]

On the other end, the courts have been allowing recovery against persons who dispense commercial services, as well as against persons who sell or manufacture a product. An example is the designer and constructor of a plant, who was held liable for injuries caused by an explosion that resulted from an improper repair of a tube in a heat exchanger manufactured by someone else.[7]

Whether the rules of strict liability apply to persons rendering "professional" services is still an open question, as is illustrated by three cases arising out of New Jersey in the three-year period between 1967 and 1969. In 1967, in a leading case, a New Jersey Appellate Court held that the strict liability doctrine did not apply to a dentist sued by a patient when a hypodermic needle broke off in the patient's jaw. The Court held that strict liability principles do not apply to persons rendering "professional" services.[8] A year later, in 1968, a federal court applying New Jersey law held that strict liability was not applicable to a company that designed, engineered, and supervised the initial operations of a chemical plant, when an employee died after inhaling lethal dust generated by the plant's operation. The Court characterized the company's acts as "professional services," and on that basis, held that strict liability did not extend to the company.[9]

Then, in 1969, the New Jersey Supreme Court held a beauty parlor strictly liable for services that caused burns to the scalp and hair of a patron of the shop. Distinguishing the case of the dentist decided just two years earlier, the Supreme Court said the dentist was rendering "professional" services, while the beauty shop was rendering "commercial" services.[10] In my opinion, this purported distinction between "commercial" and "professional" services is an illusory one that is difficult to justify. I suspect that in this age of consumerism, the case will soon come along that will cause some court to inter that distinction in the legal graveyard, along with other discredited legal fictions.

LIABILITY IN THE LABORATORY

A strong argument can be made that the rules of strict liability should be extended to apply to an environmental testing laboratory. The reasons the courts give for imposing liability on a manufacturer or seller of a defective product apply equally as well to the operator of a laboratory conducting tests using human subjects. Let's look at the reasons for imposing liability without fault, and then apply them to the environmental research laboratory.

In a pioneer product liability case, the California Supreme Court held that a manufacturer of a power lathe was liable for injuries caused to the user of the machine because the machine's defectively designed set screws worked loose while the machine was operating. The Court said, "The purpose of such liability is to insure that the costs of injuries resulting from defective products are borne by the manufacturers that put such products on the market rather the injured persons who are powerless to protect themselves."[11]

Two years later, the Illinois Supreme Court held the manufacturer of a truck's brake system liable for damages suffered by the occupants of a bus that collided with the truck when its brakes failed. The Court thought that imposition of liability without fault was justified by the following arguments:

- Public interest in human life and health call for the utmost legal protection.
- The manufacturer who solicits and invites the use of his product, by advertising and otherwise, should bear the loss caused by such use.
- The loss caused by a defective product should be borne by those who created the risk and reaped the profit from it.[12]

Other reasons advanced in support of the rule imposing liability without fault on the manufacturer or seller of a defective product are:

- Liability is an incentive to make safer products.
- The manufacturer and seller are in a better position to discover the defect than is the consumer.
- The manufacturer and seller can insure against the

risk, and recover the cost of insurance through the price structure.

On examination, all of these reasons apply as well to the environmental research laboratory that injures its human subject, as they do to the manufacturer of a product that injures a user. The human subject is generally powerless to prevent an injury sustained in a laboratory. The laboratory solicited the subject and invited him to engage in the activity that caused the injury. The laboratory, not the volunteer, profits from the activity that caused the injury. The laboratory, not the volunteer, profits from the activity. The laboratory is in a superior position to discover the defects in the system and to insure against them. And the rule imposing liability on the laboratory will promote safety-consciousness and safer experiments.

Thus, a strong argument can be made that the liability rules that govern manufacturers and sellers of products in the marketplace should apply to research laboratories whose research involves human subjects. That being so, it seems appropriate to explain what is meant by strict liability, or liability without fault.

THE OBVIOUS HAZARD: WHO'S TAKING THE RISK?

Liability without fault does not mean that liability arises every time an injury occurs. For liability to arise, the injury must have been caused by a "defect" and the concept of "defect" is a complex legal issue. In general, a product is said to be defective if it fails to meet the reasonable expectations of the consumer. Thus, the law does not impose liability when a consumer is injured by ordinary risks that can be expected. For example, a restaurant was not liable to a native New Englander for injuries caused by a small fish bone in a bowl of chowder.[13] Similarly, a shoe manufacturer was not liable to a customer who, while wearing the manufacturer's shoe, slipped on a wet floor in a laundromat, because consumers know that shoes tend to become slippery when wet.[14] However, the fact that a danger is obvious does not necessarily prevent the imposition of liability. A South Carolina court held a seller liable for injuries caused to a child whose hand came in contact with the unguarded blade of a power mower, even though the danger was obvious.[15]The Illinois case that I mentioned earlier, involving the unguarded cornpicker, is another example of an obvious hazard still subject to liability.

Thus, there is no clear rule for determining when liability may be imposed in situations where the harm was caused by an obvious risk. The test seems to be whether the risk, or danger, was unreasonable, considering the seriousness of the harm, the chances of its occurrence, and the ease with which it could have been prevented. For example, a railroad may have no legal duty, and therefore, no liability to install crossing gates on a little used country road that crosses a single railroad track carrying three trains daily. The risk of an accident is slim because there are few cars and few trains. But the risk of an accident may be "unreasonable" if the road is a highway, heavily travelled by high-speed automobile traffic, and the gate could be installed relatively inexpensively.

So, in our hypothetical example, the human subject knows that he is taking some risks. Therefore, the laboratory would probably not be liable for a temporary asthmatic condition, or for minor skin irritation, or for a sore throat caused by the experiments. These risks seem to be the kinds of risks a subject should expect. However, if the injury was permanent, i.e., lung damage, heart damage, or even death, the laboratory may well be liable because the risk of permanent health damage would probably be judged to be an "unreasonable risk."

HOW MUCH RISK DOES THE SUBJECT ASSUME?

Related to this problem of strict liability is the issue of "assumption of risk," which is often raised as a defense to liability. The rule is that a person who voluntarily and unreasonably proceeds to encounter a known danger cannot hold another liable for the injuries he suffered as a result of his actions. "Assumption of risk" means that the injured party knew of the defect creating the danger, and appreciated the significance of the danger to which he was exposed.

Consider, for example, the case of the appliance repairman who sued the manufacturer of a pressure bottle that exploded, injuring the repairman. Despite the warning imprinted on the bottle, which read, "Do not refill," the repairman refilled the bottle, which originally contained Freon gas, with oxygen, and used it to blow dust off of appliances he was working on. In the process, the bottle exploded. The bottle manufacturer settled the case by making a substantial payment to the repairman. Because the warning was sufficiently ambiguous as to the possible dangers of refilling the bottle, it was difficult to prove that the repairman assumed the risk. The warning could have been interpreted as an effort to prevent possible impurities from entering or forming in gas used in the refilled container.

In the hypothetical example, the voluntary nature of the subject's actions (i.e., the absence of pressure or coercion) may be shown by the low amount paid to the volunteer. A sum of $4.50 an hour is not enough to coerce anybody to participate in a research experiment. But the same low payment also supports the volunteer's argument that he did not intend to subject himself to the kind of serious risks that injured him. Who among us would voluntarily risk permanent health damage for $4.50 an hour?

Assumption of risk in products liability cases is tough to prove. I think that in the research situation, assumption of risk will be almost impossible to prove. A laboratory that injures a human subject while doing research on that subject to learn the extent of the danger of a substance will have some difficulty convincing a jury that the subject knew, understood, and voluntarily accepted that danger.

There is one other aspect of the law that should interest you. If the defect that caused the harm was a defect in machinery that the laboratory purchased elsewhere, then the laboratory can probably recoup the money it must pay the injured volunteer from the manufacturer and the seller of the defective equipment.

In summary, then, a laboratory is liable for the injuries suffered by a human research subject if the injury is caused by the negligence of a laboratory's employees. Furthermore, the laboratory is probably liable, even in the absence of negligence, if the injury was caused by a defect in the laboratory system, or in its operation. How can you avoid this liability? The answer is, you can't. You must learn to live with it. In the long run, the best defense is to keep the safety of your human subject uppermost in your concern. Fully disclose the risks as you see them, do your best, and buy a good insurance policy.

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13. Webster vs. Blue Ship Tea Room (1964) 347 Mass. 421, 198 N.E. 2d, 309.
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Discussion Summary

Participants considered a situation in which neither the investigator nor the subject was aware of the subject's hypersensitivity to a given substance, and subsequently, the subject collapsed in the middle of the experiment. Who would be held liable in this case? This question is one that has not yet really been answered. Some state supreme courts have held that if there was no way that the subject's hypersensitivity could have been predicted, the laboratory cannot be held liable.

However, other courts, based on the information that one percent of the U.S. population is hypersensitive, held that the experimenters should have issued some sort of warning to the subject prior to the experiment, and thus, they may be held liable.

If the situation is such that the subject would not have been injured had he not participated in the experiment, the laboratory will probably be held liable.

Participants questioned whether review board members have ever been held liable for quoting a subject's test data. In general, review boards are not held liable in this situation unless the review board itself is the entity conducting the experiment, as sometimes happens.

Other discussion focused on the extent to which a funding agency can be held liable for a subject's injury. Is a funding agency, e.g., the EPA, responsible if a subject in one of its funded experiments is injured? A funding agency can be sued, but whether the case will be won depends on the extent to which the funding agency was involved in the experiment. A number of cases in other areas of liability have exonerated funding institutions from liability. For example, in the case where a bridge contracted by the

Federal Department of Transportation collapsed, the Department was not held liable because it had little to do with the construction of the bridge, aside from a review of its size and location.

In a case where equipment furnished by the federal government to the grantee is the cause of injury, the government could easily be held liable, assuming the government agrees to be sued. In a case in New York, a sailor was injured by an aircraft carrier catapult constructed by a contractor to the U.S. Navy. When the sailor attempted to sue the federal government, the Department of Defense claimed sovereign immunity.

Although the court backed the Department's decision not to be sued, it felt that the sailor should be able to recover damages from somebody. So, even though there was no proven defect in the catapult, the manufacturer was held liable because it was the only source with money enough to pay damages. This is called the "deep pocket" theory; that is, the court recovers damages from the party with money enough to pay for the damages.

A final discussion was concerned with whether a laboratory can be held liable for long-term adverse effects suffered by research subjects. Whether a laboratory is found liable depends on the severity of the experiment's aftereffect, and whether the subject was fully aware of all the risks to which he would be exposed. If the long-term effect is not serious, chances are that the laboratory will not be held liable because the subject knew he was exposing himself to some element of risk. However, if a subject suffers serious consequences as a result of an experiment, the laboratory may be held responsible.

Nevertheless, the chances of a laboratory being held liable for the long-term effects a subject suffers diminishes with the passage of time because it is hard to trace fault back to an experiment that was conducted several years earlier.

Informed Consent—Its Function and Limitations

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Space limitations make it impossible to fully discuss all the potential ramifications of the issue of informed consent as it relates, or might relate, to environmental research. In truth, I feel an even more distinct limitation in that I do not have a full or detailed understanding of the kinds of research being conducted. Accordingly, I had to make certain assumptions.

ASSUMPTIONS AND CAUTIONARY NOTES

General Assumptions

I understand that certain tests or experiments, which have to do with the effects on human beings of certain kinds of environmental conditions, are conducted under clinical and controlled conditions. For example, I understand that individuals participating in your research might be exposed to various levels of carbon monoxide in order to determine certain human responses or responses of the human body to such exposure. I fully understand that this is only an example of the kind of research that is being conducted, but that it is, in a general way, reasonably representative of the kinds of research being done.

In addition, I made certain assumptions about why the medical profession is concerned about the question of informed consent.

In general, my assumption is that the informed consent question is important because of the ethical considerations that environmental research might raise. However, I make no pretense in that direction and I will leave these issues to those more qualified to speak on the subject of ethics. I do assume that this research is performing a valuable service for society and that researchers are interested in continuing research without incurring the societal disapproval that might come about if individuals participated without having granted their informed consent. I further assume that doctors are interested in the basic legal principles regarding informed consent so that they may avoid, as nearly as possible, exposure to legal liability for money damages to research participants. Additionally, I assume that to the extent that legal principles may be unclear so that one cannot advise absolutely how to avoid exposure to liability, that doctors nevertheless wish to have pointed up the best ways to avoid any potential liability.

Even with these assumptions, I think it would be improper and unwise for me to offer "legal advice" in its true sense about any specific procedures or problems that have been or may be encountered in environmental research. First, I do not consider myself an "expert" on the subject of informed consent in the scientific research context. Second, as I have indicated, I have not evaluated any particular areas of research nor any methods employed to secure a participant's informed consent. My perspective, then, is that I have a professional acquaintance with the legal doctrine, if we can call it that, of informed consent in general. I emphasize that I do not propose specific solutions to any kinds of particular problems, but will discuss general issues, problems, and principles as they may relate to environmental research. I emphasize, in particular, that my remarks should not in any way be deemed an adequate substitute for a detailed analysis of the informed consent problems by legal counsel employed for that express purpose.

Some Further Cautionary Notes

The development of the informed consent doctrine did not arise in the particular context of general scientific research. The doctrine arose in the context of the medical profession and involved, most particularly, the relationship between a doctor and his patient. The context out of which the doctrine developed has certain implications for our analysis.

First, since the doctrine arose in the context of the doctor-patient relationship, generally the problem concerned therapeutic procedures. For our purposes, therapeutic procedures may be defined as those procedures concerned with direct attempts to provide remedies for perceived ills of a doctor's patient. The doctor-patient relationship has traditionally been one which we lawyers speak of as "fiduciary." That word is simply a fancy way of saying that a patient places a trust and a faith in his doctor.

Second, the doctor-patient relationship, in a therapeutic context, may permit a doctor certain kinds of latitude that may not be available to a scientist/researcher conducting research in a nontherapeutic context. I refer specifically to a doctor's "therapeutic privilege" which might permit the doctor to withhold certain kinds of information from the patient in certain kinds of situations. For example, a doctor is not required to disclose a risk to a patient when disclosure of the risk to the patient would be contraindicated in light of the patient's medical condition. For the purposes of this paper, I have assumed that a scientist/researcher would not have such a privilege.

The third consequence of the nontherapeutic situation relates to the fact that persons participating in nontherapeutic research do not have an expectation of a cure or other remedy to some perceived medical ill as an inducement to participate in research nor as a justification for his participation. Accordingly, I have assumed that in a nontherapeutic context, the inducement to a person to participate in research is some reason other than an expectation of a direct, personal, medical benefit. This may have certain consequences when we speak in terms of factors that might induce one to participate in an experiment. This, in turn, may bear on issues such as voluntariness and free choice.

Also, in the therapeutic situations there are various kinds of exceptions to a physician's or medical person's duty to fully disclose relevant information, for example, in the treatment of mentally incompetent persons, insane persons, persons under the influence of drugs, persons subject to a "medical emergency," and the like. Additionally, legal issues may be raised if participants are children or minors. Since these are specialized issues I have omitted them from my discussion.

To recapitulate, I have made the following assumptions:

1. that environmental research is nontherapeutic research in which no benefit to a participant in the research in the form of a direct medical remedy is expected,

2. that this environmental research is directed toward the pursuit of important societal objectives, but that these are benefits that would flow only indirectly to a research participant, and

3. that research subjects are in all respects legally competent to grant consent, i.e., persons of sound mind who are of sufficient age to personally grant consent.

Finally, I must caution that the law of informed consent that I shall discuss is not uniform in all particulars. It is not uniform because it is being developed simultaneously in 50 different states by state courts applying what we lawyers call the "common law," and in several instances, by state legislatures. Thus, to speak of "the law" of informed consent is inaccurate. Nevertheless, there are certain general principles to which we can refer with fair accuracy for our purposes. But complete accuracy would require analysis of the cases and laws of the states where the research is conducted.

HISTORICAL PERSPECTIVES ON THE CONSENT ISSUE

With these assumptions and cautions in view, let us now turn to certain historical perspectives on the consent question, since this may "inform" our consideration of its application in modern contexts, such as the scientific research context.

No doubt, the foundation from which we derive our current doctrine of informed consent can be traced rather directly to the law's very early recognition that "every human being of adult years and sound mind has a right to determine what shall be done with his own body." This statement, which is general in the law, recognizes the human being's right to self-determination and personal autonomy.

Accordingly, it was very early in its development that the law recognized that any interference with personal integrity or with the "inviolability" of a person's body is a violation that the law is prepared to remedy by assessing damages. As a corollary of this right, there naturally had to be developed a doctrine stating that if a person consented to an invasion of his personal integrity, which otherwise would constitute a legal wrong, the very existence of that consent precluded the invasion from being wrongful. As illustrations, we can quickly see that a punch in the nose is an offense to one's bodily dignity if it occurs between strangers on a street corner. Conversely, we can quickly recognize that precisely that same punch in the nose when it takes place in a lawful boxing match does not expose the person doing the punching to liability. It was precisely the central concept of personal dignity and bodily integrity that gave rise to a doctrine in the law of torts that is known as "battery" (or sometimes inaccurately referred to as "assault"). The "black letter" definition of battery is "any intentional touching of another which is harmful, or offensive to a reasonable person."

The ingenuity of human beings to vary their conduct naturally required further development of this legal doctrine. For example, consider the case of a person who went to the hospital for a checkup, who was approached by a doctor, placed under anesthesia, and then operated on. For example, let us say that the person's appendix was removed. Now clearly this is distinguishable from a punch in the nose between strangers on a street corner. But is it nevertheless an invasion of the person's bodily integrity if the person was not in the hospital for the purpose of having his appendix removed and had authorized no one to undertake such a procedure? The problem is that the doctor in question was not actuated by any evil intent or desire to do harm. That, however, was not essential. The courts had no trouble finding that the operation in those circumstances was an invasion of the person's bodily dignity, because the "invasion" occurred without the consent of the person on whom the operation was performed. That person could sue the doctor in a torts action for battery. In other words, because the touching was not consented to and because in the absence of consent it was wrongful, it exposed the one who did the touching to liability.

Similarly, we can imagine instances in which a man represented himself to a woman as "a doctor," secured her consent to a physical examination, and proceeded to perform that examination. The woman subsequently discovered that his statement that he was a doctor was true, but that in fact he was a Ph.D. and not an M.D. When this situation arose, the courts had little trouble in finding that, of course, consent to the touching had been granted, but that it had been granted pursuant to fraud or misrepresentation and was completely ineffective. Naturally, that would lead to the liability. It may be instructive to point out, based on the preceding hypotheticals, that it is immaterial whether the patient operated on in fact needed his appendix removed or whether the doctor who removed the appendix had done so with every degree of skill and care. Similarly, it is irrelevant whether the Ph.D. knew how to conduct a physical examination and did so with every possible skill. The nonconsensual removal of a bodily organ, even diseased, would violate the very principle that without consent the touching was unauthorized, and without any consent to the touching, it was unlawful. So too would the physical examination be considered wrongful where the consent had been obtained under false pretenses.

Over the years, other situations developed. The classic case, perhaps, is that of a woman who went to the hospital and consented to an operation on her left ear. When placed under anesthesia for that purpose, the physician discovered that her right ear needed the operation more than her left, and proceeded to ignore the left ear and operate on the right ear. Without any allegation that the operation was not performed skillfully in every respect, the plaintiff sued the doctor and contended that he had no consent to operate on her right ear. The court agreed. It held that the operation on the right ear was indeed an unlawful invasion of the plaintiff's body, and was a battery because it was done without the plaintiff's consent. The question naturally could not be avoided whether indeed the plaintiff had not consented to an operation of the precise character as the one performed, except on another part of her body. It could be suggested that the plaintiff had given consent to an operation, which was true. The consent, however, was limited to an operation on the left ear. Out of this we derived the legal principle that consent may be granted but that the consent must not be exceeded.

Then cases arose in which, for example, a patient had consented to an "exploratory operation," and that in the course of the operation the doctor removed a diseased organ. Having consented to the "exploratory operation," the issue naturally arose as to whether the plaintiff also had not consented to the removal of the diseased organ. The doctor thought "exploratory" meant "if you find a disease do what in your medical judgment seems indicated." The plaintiff thought "exploratory" had its common meaning of "look and see." Since patients are medically untrained, the courts came to the position that it was up to the doctor to make sure the patient understood what was meant if the terms used had meanings other than those that untrained lay persons ordinarily would accord to them. In many cases, except those in which life or serious consequences might be threatened by failure to remove the organ discovered to be diseased, the courts did not hesitate to find that the removal of the organ without the patient's consent did indeed violate the principle that every person had a right to determine his bodily integrity. Generally speaking, the courts that looked at the problem in its early stages considered this matter to be a battery.

Then a series of cases arose in which the patient consented to a medical procedure, and that procedure was carried out with skill and competence, but, for example, the incision did not heal, some other organ was damaged during the operation, or the patient contracted a disease as a result of the operation. The courts had some trouble with this problem in that the patient had consented to the precise procedure undertaken, but it had not produced the results that both the patient and the doctor reasonably expected. While each person reasonably expected positive results, by reason of medical training and skill, as well as experience, the doctor knew that in certain kinds of procedures risks exist, for example, certain complications occur with a more or less statistically predictable frequency. The patient had not known of these risks. The earlier cases to rule on the problem found that the failure of the doctor to disclose potential risks of the procedure, of which he was aware, vitiated the consent granted by the patient. Upon holding that the consent was not effective, it followed that a battery had occurred.

Beginning around 1960, however, courts began to recognize that the problem did not really involve an invasion of the bodily integrity without consent. Nevertheless, they were mindful of the notion that originally gave rise to tort of battery—that an individual ought to be able to exercise self-determination with respect to his own body. Accordingly, the view began to be developed that the real problem was not the absence of consent but that that consent had been granted upon inadequate or insufficient information about the risks or potential complications of the treatment. The courts found implicitly in these situations that the patients had relied on their doctors for information and the doctors had failed to provide enough information. In this light, the problem did not look like battery, which we saw earlier as a punch in the nose between strangers on a street corner, but more like a problem arising out of the nature of the relationship between the doctor and the patient.

When the doctor failed in that relationship, in areas not involving an absence of consent, the failure was treated as "malpractice." Malpractice was in another branch of the tort law called "negligence." This treatment of the problem had certain legal consequences which I will omit since they are not directly germane to our discussion. Suffice it to say that the courts began to impose on doctors a duty, premised on their relationship to the patients, to inform patients of all the material information that would be necessary to enable patients to make an informed judgment as to whether or not to undergo a medical procedure. While not every court would articulate the analysis this way, in general, we may say that courts understood that the physician was an expert and the patient was not, that patients continued to have an exclusive right to exercise control over their own bodies, that consent premised on inadequate information was not fully informed, and that the patient was in complete dependence upon, and must trust in, the physician to provide information necessary to an intelligent and informed decision.

Based on these considerations, one of the leading cases on the subject decided that the law should impose a requirement upon a physician to present to his patient all information relevant to a meaningful decisional process. Of course, the physician, by reason of his training and experience, could make an evaluation satisfactory to himself or herself. But the court's judgment was that the decision was not the physician's to make. It was the patient's!

It was in this context that the failure to disclose relevant information was treated as a malpractice problem, that is, a breach of a physician's duty to his patient.

DEVELOPMENT OF THE INFORMED CONSENT ISSUES

General Statement of the Doctrine

A general statement of the doctrine that has come to be known as "informed consent" may be attempted. The informed consent doctrine provides that a doctor must provide a patient with sufficient information to enable that patient to make an informed and intelligent choice as to whether to undergo a particular medical procedure. When necessary to an informed and intelligent choice the information provided, generally speaking, must include the nature and magnitude of the direct risks attendant to the procedure, the methods and likely results of the procedure, the alternatives, if any, to the procedure contemplated, and the nature and magnitude of any collateral risks associated with the procedure. Failure to provide such information will make the doctor subject to liability if a risk which was not disclosed, but which could have been disclosed, results in harm to the patient, if the risk were such that if disclosed the patient would not have consented to the procedure.

Elements of the Doctrine

Having once made a general statement such as that above, it nevertheless becomes necessary to identify the precise parts or elements involved in the general statement and then we must attempt to apply those elements in the context of scientific research.

Upon analysis, we will notice that the doctrine requires (1) that certain information be provided, (2) that the person granting the consent have an ability to understand and appreciate the nature of the information provided, and (3) that a willingness to undergo the procedure be voluntarily expressed. Accordingly, we may speak of the elements as "information providing," "use of information," and "voluntariness" of consent.

With respect to information providing, in the context of medical research, it would appear clear that information regarding the procedure and methods of the research must be provided. But that is not all. The doctrine of informed consent relates particularly to the providing of information about the known risks to which one may be exposed upon participating in the research. Any known risk of death or serious bodily harm must be provided, probably in every instance.

However, it appears that more information needs to be provided. Probably every potential adverse consequence of significance ought to be disclosed. However, in the context of environmental research, it is precisely the purpose of the research to identify risks that may be involved in a particular kind of environmental exposure. Thus, it seems that a clear and positive statement should be made of the extent to which risks of the research are unknown, together with a statement of the researcher's best judgment as to the nature of such unknown risks, as well as the magnitude of the possibility of any of the unknown risks coming to fruition. It clearly seems possible that scientific research may be involved with risks that are unknown and that, in the exercise of ordinary care on the part of the researcher, cannot be known. Thus it seems very likely that a failure to inform any participant in such research that there may be risks that are unknown would constitute a failure to provide adequate information.

The second element dealing with the subject's ability to use the information provided relates simply to making the information available in a form that is understandable and comprehensible to the subject participating in the research. For example, if the subjects are lay persons, the use of scientific terms that might not be understandable ought to be avoided, or if not avoided, scientific terms ought to be defined in lay language. For example, there is a case involving a doctor who informed his patient that he wanted to do certain kinds of exploratory surgery for cancer of the breast. At the hospital the patient was given a standard form which indicated the procedure to be a mastectomy. The patient, remembering the doctor's description of exploratory surgery and not understanding the definition of mastectomy, signed the form. During the operation the doctor discovered that indeed the breast was cancerous and removed it. The court held that the doctor could not rely on the patient's signing of the standard form of consent, notwithstanding its use of the term mastectomy, because the patient had no understanding of that particular term. It went on to hold, therefore, that her consent was not an informed consent.

This is instructive in two respects. First, as indicated, the information must be provided in a form that is usable in light of the researcher's knowledge of the subject's education, training, language limitations, and similar factors. Second, the mere signing of a form will not necessarily protect the doctor, although the form itself in all respects may be adequate. This may be because the subject does not understand the terms in the form, or perhaps, because the subject did not properly or attentively study the form. In such a case, a serious question will be raised as to whether the consent granted was informed, notwithstanding that the subject signed a standard form of consent.

At this point I would emphasize that a form is a limited device. Generally speaking, a form is nothing more than a memorial of the meeting of the minds of the researcher and the subject. It is no substitute for the direct, personal provision of information. This does not mean that signed forms are not important. They are. They may be evidence of the information provided as well as the consent granted. They should not, however, in all cases, be treated as a substitute for a more effective method of providing information.

The third element of the doctrine of informed consent relates to voluntariness. Voluntariness connotes, of course, a free-willed determination, on the part of the subject, to participate in the research. Naturally, coerced consent would not be effective. Coercion, of course, would exist in the case of a person who simply overpowered a person's free-willed exercise of determination by threats or force. But coercion may come about in many, many other ways. However, the greatest concern ordinarily in a research context would not be about direct coercion, but about, what I shall call, "coercion in the circumstances." This relates to who the participant is and the circumstances that surround a granting of consent.

Some studies have investigated why people agree to be research subjects. In the case of doctor-patient relationships, in a therapeutic context, participation may come about because of the trust and confidence the patient has in the doctor. I have assumed no such motivation would exist on the part of the participants in environmental research. I have assumed that these participants may be public spirited persons, needy persons, or persons who for some other reason are influenced to become subjects. I imagine that the inducement to participate in environmental research is probably monetary. While I think significant problems of voluntariness are not likely, researchers might want to keep in mind the nature of any inducement they hold out in light of the circumstances of the persons who might choose to participate. It is not inconceivable, although I think the possibility is remote, that the voluntariness of a consent might be questioned if subjects are persons who are in such dire financial needs that the exercise of free will may be precluded by the very circumstance of their need.

Application of the Doctrine in Research Situations

As I interpret the informed consent doctrine in the context of environmental research my advice would be that researchers provide their subjects with "all the information a reasonable person would want and need to know in order to make an intelligent and understanding determination of whether to participate as a subject or not."

Who is a "reasonable person"? While that inquiry seems simple, its explication is somewhat more difficult. For the purposes of environmental research, I would think there is a soundness in the assumption that a "reasonable person" is a person of ordinary intelligence, who possesses all the data that ordinary persons in the community possess. If you are dealing with other kinds of persons, the problem would become more significant. The concept of the reasonable person has a direct relevance to the first element of the doctrine of informed consent dealing with information providing. It is probably sound to suggest that information need not be provided about things that a person in the community who has a sound mind, ordinary intelligence, and the average capacity for understanding would already know. I am not sufficiently knowledgeable about environmental research to know the exact implications of that statement. I would stress, however, that researchers should provide any information that a person of ordinary intelligence and common understanding in the community would be *un*aware of. I would generally include in this any risks of the research, the procedures, the methods, and any other information about the research that would be useful to a subject in determining whether to participate in a research project.

In connection with the precise content and detail of the information that needs to be provided, the courts have formulated a doctrine that all "material" information should be disclosed. What is "material" information? In an oversimplified way, it is any information that the reasonable person would consider important and want to evaluate in making a determination whether to become a subject in your research. For example, I think a court would be likely to hold that the possibility of a risk arising, a risk as low as one percent, if that risk would expose a person to death or serious bodily injury, is a "material" risk that ought to be disclosed. When the risk is one that does not involve a risk of death or serious bodily injury, the question is somewhat less clear. However, *any* risk that is known and would be significant should be disclosed, even if the risk is one that threatens only short-term discomfort of even a nonserious nature. I have already indicated that the very fact that certain risks *may be unknown is itself* a risk that ought to be disclosed.

I think most courts would apply the standard that a risk, to be material, has to be a risk that would be material to a reasonable person. In thoroughness, however, I should mention that some courts might hold that it is not a risk that would be material to a reasonable person, but a risk that would be material *to the person undergoing the participation in the experiment*. There is, of course, a problem here in that after a risk has come to fruition and injured a participant, that participant has every incentive to say that if the risk had been known, he would not have participated in the research.

In the medically therapeutic treatment context, there is a division of authority as to whether the standards that govern what information should be disclosed is a standard to be determined by the court as a matter of law, or a standard that is determined by what the medical profession would regard as the professional standard for disclosure. The way the problem practically arises is as follows: Let us assume that in a research procedure a certain risk was not disclosed. The plaintiff would claim that the risk was a material risk. The researcher would counter that it is not the practice in the research profession to disclose such a risk. The question then is whether the standards of the profession should control what disclosure should be made or whether the court, as an independent matter, will determine what information should be disclosed.

In my judgment, the sounder and safer alternative for a researcher is to disclose all information that would be material to a reasonable person. By disclosing all the information that the researcher reasonably can disclose, the researcher avoids the possibility of failing to disclose something even competent researchers would not generally disclose, but which later might be determined by a court to have been something that should have been disclosed.

Ultimately, it appears that there are three resolutions to the problem of what should be disclosed. There may exist an ethical ideal of disclosure, a practical limit of disclosure, and a legal limit of disclosure. Presumably, the ethical ideal would require disclosure of everything. It may be practically impossible to make an ideal disclosure for many reasons, one of which is probably related to the researcher's time and capacity for making disclosure. Whether the maximum that could practically be disclosed is the legal minimum that must be disclosed is undetermined. It would be my advice, however, that to avoid a failure to disclose the legal minimum, a researcher ought to strive to provide as much information as is practically possible in view of all the circumstances of the situation. The ultimate legal determination undoubtedly will rest on what the researcher "reasonably could have done in the circumstances."

I now turn to the question of when a failure to disclose will result in liability. We may now assume that in a particular case there has been a failure to disclose a risk that a reasonable person would regard as a material risk, and that it was possible for the researcher to disclose that risk. Speaking practically, not every failure to make a disclosure will result in liability. A failure to disclose a risk will result in liability only if an injury is caused to a person by the risk that was not disclosed. The problem is that in advance the researcher cannot determine whether a particular risk will result in injury to the research subject. By failing to disclose a risk a researcher would be taking a gamble.

One other situation in the research context that might arise involves the following situation: Assume a researcher makes a disclosure of all the risks that he knows about, discloses the fact that certain risks are unknown, and after the research is under way, gains additional information that the subject, as a reasonable person, would desire to know. Is there a duty to disclose information discovered after the experiment is under way? I am not aware of a case that has addressed this question. However, it would be wise, I think, for the researcher to regard himself as under a duty to make a disclosure at any point during the process of the research if he learns of risks that were previously unknown or learns of risks that are greater than, or different from those disclosed.

One final matter that I think should be touched on deals with the question of whether a person must be informed at the outset, as part of the researcher's duty to make a full disclosure, that he may at any time withdraw from the experiment or the research program. No definitive answer can probably be given based on previous cases. However, it is reasonable to assume that if a person has an initial right to participate or not to participate after full disclosure is made, it seems likely that the right of non-participation continues throughout the process of the research, and that a person may withdraw at any time and must be informed of the right to do so.

Situations are imaginable, however, where the withdrawal of the subject will have serious consequences to the validity of the study being undertaken and may impose a serious burden on the researcher. My best judgment is that these are burdens and disadvantages that researchers must be prepared to tolerate.

SOME PRACTICAL DIMENSIONS

Without intending to suggest that the case law would require the following things that I shall mention, I would raise these additional matters for consideration.

Who should make disclosure in a particular research program? It would probably be wise to have a person designated as responsible for providing information to participants. The practical reason is that such a procedure will avoid the possibility that one person will think another has given the appropriate information and that other person will be thinking someone else has done it. The consequence, as you can see, will be that no one would have given the information. This situation has arisen in instances, for example, in which the doctor thought the hospital would provide certain information, and the hospital, in turn, relied on the doctor to provide the information. The consequence was that the patient was not informed. A breakdown in the procedure for providing information will not justify a failure to provide it.

When should disclosure be made? It is not clear when disclosure should be made except to say that it must be made before the research begins. However, the provision of the information after the subjects are all assembled and are ready to undergo the research experiment may constitute a coercive circumstance in itself. No period for reflection, consultation with others, or sober evaluation of the information provided may be available when the onset of the research follows too quickly after the provision of the information. Accordingly, it would probably be sound practice to provide a reasonable interval between the time when the information is provided and the time when the person is asked whether consent is granted. Perhaps no fixed time limit can be stated. The overall circumstances would obviously be relevant. As a general rule, it would probably be safe to say that it would be good practice to permit a person whose consent is sought a sufficient amount of time between the providing of information and the request for consent, to permit the person to digest and reflect on the information provided and to make a sober and detached judgment about participating.

What about institutional review procedures? While it is doubtful that the existence of in-house procedures would avoid liability in circumstances where failure to disclose information has occurred, practically speaking, it would appear that the existence of in-house review panels, peer review groups, or research evaluation teams would be helpful in two ways. Institutional review procedures would make it more likely that all the relevant areas in which information can be provided are known. Second, review procedures act as a check on the researcher's own interest in carrying out research that might cause the researcher to take shortcuts with respect to the provision of adequate information. It may well be that the researcher's interest in conducting the research puts the researcher in a situation where something of a conflict of interest exists with respect to providing full information, particularly if there is reason to suspect that the provision of full information might well hinder the assembly of subjects to participate in the research.

Accordingly, as a safeguard against the possibility of the researchers taking shortcuts, which may result in a failure to disclose, it would be good practice to have such review procedures. It can be seen that the review procedures relate to the relationship between the researcher and the research institution. Arrangements between the institution in which the research is undertaken and the researcher cannot ordinarily be thought to affect the relationship between the researcher and the participants.

What is the relevance of federal, state, or other legislation? Compliance with statutory requirements may well have a direct bearing on the reasonableness of the researcher's conduct in disclosing or not disclosing certain kinds of information. It would be sound practice to scrupulously comply with any statutory requisites. It is possible that failure to comply with statutory requisites may give rise to an argument that the compliance failure itself establishes the unreasonableness of the researcher's actions.

What about federal agency regulations? The same thing that can be said about compliance with statutory requirements can be said of compliance with various applicable regulations of agencies. In addition, it may well be valuable to follow requirements of agencies that are administering the various kinds of research, because it may be that such guidelines or regulations will have been drafted by those who are thoroughly conversant with the issues of informed consent, and that by following them, the researcher will render less likely any liability for failure to meet the case law requirements regarding the informed consent.

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Discussion Summary

Participants discussed whether increasing a subject's pay as a project progresses would be construed as a way of pressuring a subject to stay with a study until its completion. Discussants said that this procedure generally would not be considered coercive.

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Role and Function of Committees on Protection of Human Subjects in Research

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As chairman of the Committee on Protection of the Rights of Human Subjects, I can assure you that membership is associated with problems. Therefore, I would like to discuss the problems of such committees as ours.

I would like to quote from a recent issue of the American Bar Foundation Research Journal, in which Benjamin Duval states quite clearly one of the problems that a committee has, in that, "...an institutional review board is in itself a legal institution." The act that called for the establishment of these institutional review boards stated that the Secretary of Health, Education and Welfare must require the establishment of an institutional review board for every entity that receives funding. Therefore, although review boards are instructed not to approve proposals that will invade any subject's legal rights, the interests protected under such regulations are significantly broader than the legal rights of the subject. Benjamin Duval makes an interesting comparison when he says that institutional review boards combine the elements of an administrative agency and a jury. They also act as a legal authority to carry out laws and also to make laws.

With that introduction, I can describe our committee's problems and methods by giving a brief outline of the methods we use at the School of Medicine at the University of North Carolina. We began our committee about five and a half years ago. Before that time,

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the functions involved in institutional review had been carried out by a committee that was in charge of the Clinical Research Unit. Because of an increasing workload, there was an obvious need for a specific committee to act as an institutional review board. Comparable committees exist in five other schools within the University. So, our committee was formed to function specifically as a medical school committee.

Our committee's purpose and principles are best described in our Document of Assurance to HEW and in some words from the Articles of Implementation. We feel that our function, as specified in our Document of Assurance, is to "fully protect the rights and the welfare of all subjects who participate in research, in investigations, in study, in development, in demonstrations, or in other projects." Obviously, this includes many direct involvements, such as the action of drugs, medical and surgical procedures, and so on. But our committee has extended its responsibilities further than this, for example, to include non-invasive observations and data collection. We are concerned that there not be undue invasion of the subject's rights to privacy, and that there is no undue risk to the subject, at least not physical risk. The same is true of moral rights.

One of the first obligations we had was to inform the faculty that if they plan to do human research, they must have their work reviewed in advance. Oftentimes, the investigator is reminded of this obligation when his funding organization will not consider his application until it has been reviewed by a board.

Our primary obligation is to look at human rights, and not at the scientific merit of a research proposal. This is impossible because usually we must consider both aspects. If someone submits a frivolous scientific experiment, we would not accept it if there was any type of risk to the subject. On the other hand, there are times that the scientific merit and the amount of medical information to be gained do warrant some risks, and the experiment thus would be acceptable. We must in all cases have a balance between the two considerations, although the question of scientific merit is not our specific concern. Finally, we feel that one of our serious obligations is to make sure there is no undue enticement to persuade a patient to continue an experiment against his wishes.

One of the other principles that we work under is that we feel that this is a serious committee, and therefore, it should have the representation of the most experienced and the senior faculty. Presently, the people who are on the committee, with only a couple exceptions, are people in senior positions at the University. We use these people, not because their age necessarily implies wisdom or good judgment, but because they are familiar with the University. They are also familiar with the investigators and have their respect, so that if we on the committee disagree or need to advise the investigator, this guidance will come from a body that speaks with a certain amount of authority.

Other important members of our committee are the representatives of the public. I think, probably, we should have a greater representation from the community, because the people who work on a voluntary basis, the public representatives, do an exceedingly good job. In reviewing research proposals using human subjects, the public representatives approach this task with a completely different point of view than we do, and oftentimes, they make very important judgments or find problems that we with our bias of a medical education, with our bias of seeing patients and subjects all the time, would have missed. We are not legally required to include public representatives on the committee, but including representation from the public or from the community is very strongly recommended.

We differ from other institutional review boards across the country. For example, our committee meets only on a few occasions a year, and we do most of our review by mail. We do most of our voting by ballot. One of the reasons why we operate this way is because of the volume of our work. In a three-year period, we reviewed 297 new proposals; we reviewed for re-review 398 continuing proposals, or 695 proposals during this period of time. This comes down to four or five proposals a week, 19 to 20 a month. I could not keep people on the committee if we convened twice a week to discuss these proposals, as we would have to, or once a week. I could not ask the representatives of the community to meet with us that often. This is the first reason why we do most of our work by mail review and by balloting.

I think there are some advantages to this work procedure. In general, a proposal comes to my office when it has been reviewed by the principal investigator's departmental chairman. It is then reviewed by my staff for completeness to see that all the forms are in. There is a consent form and there is a review of the proposal. At some time this proposal may be given administrative approval. This is a right that has been given to me by a local committee. An illustration of administrative approval would be a proposal that has been approved, but has not been funded. Thus, the proposal has not been active, and the investigator wants to continue the approval process. The committee allows me to give administrative approval in other similarly benign or uncomplicated situations, but they in turn review at the next meeting of the committee all of my administrative approvals and sanctions, and in some cases, they deny approval.

Once a proposal is reviewed for completeness, it is sent to a subcommittee, and all the information that is sent to me, all the documents that come in for the research proposal, go to a subcommittee that goes through this package in depth. Then they report back to us. If the subcommittee reports a unanimous vote of approval, there are no problems, and a simplified form is sent to the full committee, who in turn ballot back again. If, however, the subcommittee says there is some problem; for example, if they are concerned about the use of human subjects in the project, then an ad hoc committee of experts in the appropriate field is appointed to review the proposal with the principal investigator.

Now, I, as an obstetrician, cannot be expert on cardiac problems. Our surgeon is not an expert on pharmacology. Therefore, we use members outside of our committee, and at times, outside of this University, to serve on the ad hoc committee to review with the principal investigator the proposal and to try to decide about the sticky problems. The subsequent report in turn comes back to the full committee, who now ballot by mail. They have the right to either accept the proposal, to request modification, or to reject the proposal.

It has been decided that no research activity will be rejected without a majority vote, and that no research activity will be accepted without a majority vote. Actually we usually work on a unanimous vote. If I see that 12 members on a committee have accepted a research proposal, but one person picks up a very important but overlooked infringement of the rights of a human subject, then we will turn that proposal down, because I think we must lean over backwards to protect the subjects, even though the vote may have been leaning the opposite way.

One reason why I like the idea of the mail ballot is because instead of having to make up your mind in a committee meeting at five o'clock on Friday, you have the opportunity to make up your own mind when you want to sit down and review these proposals when you feel like it, when you can give the time to it, and when you reach an adequate decision. So, I do feel that the balloting method is defensible, and we probably get better reviews than we would by sitting in a committee as a group. We do sit in a committee as a group at regularly stipulated intervals, for example, when there is any division of opinion about a proposal, or when we need to speak to the principal investigator.

The final decision of the committee is final and it is not questioned by higher authorities within the University. I think it is stipulated by certain regulations that if we turn down some research activity, there cannot be pressures from the Dean, the Chancellor, the Vice-Chancellor, or from anyone else to change our decision.

PROPOSAL REVIEW

Out of 297 research proposals, we rejected only three. I think this is to the credit of the faculty at the University. They now recognize, not just because of the threat of legal liability, the importance of human life. They do not submit research proposals that infringe upon the rights of human subjects or endanger their health in any way. When we did request modification of 31 proposals, we were primarily asking someone to take out a risky portion, or what we considered to be a risky portion of their research proposal, or we asked them to modify their consent form, or, in some cases, an application was incomplete. If we had not requested and given the principal investigator opportunity for modification, we would have rejected more proposals.

One of the problems that the committee has is the amount of work. Another problem we have is overlapping with jurisdictional problems between one school of the University with another. What if a proposal is a combined research activity between the Dental School and the Medical School; between the School of Nursing and the Dental School; who has jurisdiction? That question has not been solved yet and it has been a sticky problem, but I think it is an administrative problem.

One of the other problems is, and I am not going to quote this directly, that the HEW regulations regarding review committees state that no matter how distant the research work may be from the granting institution or from the institution receiving the grant, that institution is responsible for protecting the rights of these research subjects. This regulation became very important to me a couple of years ago when we were funded for some research activities in Chapel Hill. Those monies were being spent in India, in Pakistan, in Iran, and in a number of European and Asian countries. We were legally responsible to those subjects in Charez. It was up to us to make sure they understood the consent forms they were signing—an almost impossible thing to do with any guarantee of completeness.

This is a problem that is not only concerned with research conducted out of the continental United States; it is also a problem in cases where someone is doing research where part of the research subjects are located in a distant city, or when they are at a distant hospital. Do they use what we think is a consent form, or what they think is a consent form? So far we have insisted that our consent form be used since we are responsible for research subjects. It is a problem for other institutions, other schools in the University that want to use patients of the medical school hospital. A professor of anthropology would like to talk to cancer patients to examine some aspect of their psychological reaction to their disease—can he do this? Who reviews his proposal? How about those people who just want to use record room reviews? Is this, even though they do not identify the subject, appropriate to do?

ETHICAL PROBLEMS AND POLICIES

Another difficult problem that is unsolved is the use of excess tissues and fluids. Someone says, "Well, when you send a tube of blood to the laboratory, they are going to use just 1 ml. I would like to use the other four. I do not want to get consent from the patient. I just want to look at the blood. I do not have to know who the patient is. I am not going to give any feedback to the patient. The blood is going to be thrown away anyhow." At first the idea sounds like "why not?" But you find that soon, the same person says, "A little extra blood is all right, but why don't you get another tube when you collect it? It won't hurt to get more than the one tube." Then you see you are infringing on a human subject. You are not going to harm him very much, but two tubes become four, or a little more cerebrospinal fluid. If you are doing some biological or pharmacological or biochemical test and you find that one of your samples now has evidence of some serious disease, do you have the right or the obligation to go back and search out that patient to tell him that he has some serious disease? These are some of the ethical problems that we have had, and we do have. We have not completely answered them. Finally, one of our present problems is that we review all human research done by the faculty of the Medical School. How about the research that is done on the patients of the hospital associated with the Medical School, that is not done by faculty? Who reviews that human research? It looks like the committee is going to be asked to do this.

Another problem is concerned with the civil legal liability of the members of the committee. We have looked into this matter and we have known no instance when members of the committee have been held liable. But we have within this University one school whose faculty has suggested not serving on a committee until they have some liability insurance protection. I do not know if their threat is going to continue. The Chancellor's office has responded by saying that they will look into getting insurance for all of us who serve on such committees. That process is going on now.

A final problem is, what is research? We say that we review research on human subjects, but where is the dividing line between clinical care and research? We change our methods of doing a medical procedure--and I have to use an obstetrical example. If we decide that all breeches should be delivered by Caesarean section rather than vaginally, and we keep a record to see how it works out, is that considered research, or is that just observation of what we hope is improved clinical practice? This is a difficult decision. Do you have to go to that patient and say, "You have a choice between a vaginal delivery and a Caesarean section"? Obviously, she cannot make that choice.

Another problem we have is, when does research become accepted practice? Again, for obvious reasons, I use examples in the reproductive field. One faculty member developed a clip for sterilization—obviously this was research. He wanted to see how successful the clip was, how many pregnancies resulted when this clip was used, was it better or was it worse than other contraceptive methods. After a period of time, he looked at a thousand or so subjects and said, "Well, my next thousand subjects—will they be considered as research subjects or have I already done the research? I know there were three pregnancies in the thousand, and the clip is available clinically now." He says, "I am still going to collect data on the clip because I am not sure how it is going to work out. It has not been tested long enough yet, but it is commercially available." When does research become accepted practice? What about informing patients who have unexpected results or abnormal findings? Is it the investigator's responsibility to tell that patient?

ADVICE AND CONSENT

Finally, our biggest problem is with consent forms. First, I dislike the term "consent form." I do not think there should be a form for giving informed consent. There cannot be a standard form for an institution. There cannot be a standard form between different research activities. I think each consent form should be written in a language that the patient understands. This is where we can use our community members on the committee. If they cannot understand the consent form, then I am sure the patient cannot. The patient should understand what is being done, the benefits, the risks, the discomforts; whether there could be an alternative procedure other than the research procedure.

Then, we ask that it be included in the consent form that the subject is free to withdraw from the experiment without penalty. We try to serve as the research subject's advocate by saying that in the consent the subject should be told that if he feels his rights are being threatened, he can contact the Committee on the Protection of Rights of Human Subjects. The consent forms have to comply with the laws of this state, which may not be the laws of another state.

Yesterday I received two research proposals. One consent form had three lines. It said the investigators were going to withdraw blood, 5 ml, and the patient is supposed to sign. That is about all the form said. It was not written in the first person. I think if you are going to consent to something, the consent form has to be written in the first person.

The other consent form, believe it or not, was fourteen pages long. I think this is equally bad as the three-line consent form. I am not sure how many subjects will wade through fourteen pages to give consent to some research activities. I am afraid the committee may be at fault for pushing investigators to make sure that all the essential elements are on the consent form—we have made them make it quite voluminous.

Finally, we do not like to act as a threat to the investigator, but rather, we like to act as a protector of the research subject. We are also protecting the investigator, not necessarily from any legal liability, but we are protecting him by helping him realize the rights of human subjects.

In spite of regulations made up by committees, I am sure that research is going to continue. I am sure that research will continue with human subjects, no matter how much basic or animal work can be done. New procedures, new agents must be tried on human subjects at some time. I think the continuation of review mechanisms such as ours will remain, and must remain, in existence for as long as they remain reasonable and acceptable. Finally, the most important thing in all circumstances is that the subject must be informed adequately before he gives consent.

Discussion Summary

Participants discussed the advantages and disadvantages of having obstreperous members on review committees. On the positive side, participants felt that those who are apt to be meticulous about every point discussed in a committee meeting may bring up an issue that has been overlooked. A disadvantage is that this type of committee member may tend to disagree simply for the sake of disagreeing. In this case, some committee chairmen have the prerogative of deeming a committee member's objection as "unacceptable."

Participants also discussed the need to keep bureaucratic overload in committees to a minimum. Discussants felt that staff review of research proposals is justified in that these reviews reduce the amount of time spent considering proposals that are obviously unacceptable or missing required forms.

METHODOLOGIES AND PROTOCOLS IN ENVIRONMENTAL CLINICAL RESEARCH

Moderator: Ralph Stacy, Ph.D.

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Developing Methodologies—Environmental Studies

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I would like to discuss a number of problems associated with the development of methodology, primarily from the non-invasive standpoint of investigating man under conditions of stress, whether the stresses are combined or single stresses. I would like to emphasize that most of our new procedures have been designed to work in multiple environments and under multiple stresses.

CHARACTERIZATION: A PRE-TEST PROCESS

I would like to start off by reviewing some of the basic things you do before developing a methodology. The researcher must effectively characterize the subject so he knows just exactly what he is going to do, what he is going to work with, and what he is going to do for the research subject from the standpoint of assuring that he has adequate safety in all of the procedures that will be employed.

Sensitive Subjects

Researchers have to contend with the problem of sensitive subjects and how you determine whether sensitive subjects are going to be in your pool, and what you are going to do with those subjects after you have them in your pool, or, in some cases, whether the researcher should set out to select a group of sensitive subjects

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among a so-called normal population—not to look at individuals with disease, but individuals who are essentially considered to be normal in physiological terms, in both their pulmonary and their cardiovascular systems.

Actually, we have had a problem with sensitive research subjects, because in almost all of our studies we have found one or two subjects who were sensitive to the particular pollutant that we were studying. In retrospect, it appears that we could have determined the subjects' sensitivity by using a questionnaire. If you are going to study sensitive subjects, you should have those subjects available to you as sensitive subjects, and not have to include them as part and parcel of the overall population.

Work Capacity

A number of techniques of carefully categorizing an individual have been developed over the years. One of these techniques has to do, especially in air pollution studies or in toxicological studies, with evaluating the potential capacity of the subject to perform work. It has become apparent that one of the major factors in the response of an individual to a pollutant is whether or not he is active or inactive. Many of the studies that have been done on environmental pollution have used resting subjects, and have consequently missed the value of or the importance of the role the pollutant will play in the response of the subject, because most subjects exposed in a natural environment do have to work.

The first evaluation of any subject has to do with his potential work capacity, and there are several ways that this work capacity can be measured. The best way, since almost everybody can walk—and this applies to individuals of all ages, anywhere from six to eighty odd years of age—is to measure their maximal aerobic capacity by having them walk on a treadmill that changes its rate. The treadmill can maintain a constant speed or it can change its speed, as well. You can perform this test very simply by a relatively straightforward technique. A computer gives the test results out immediately, so that you know not only the subject's ventilation, but also his oxygen uptake, his CO_2 production, his body temperature, his heart rate, and his electrocardiogram as it is measured.

Another procedure that we use to measure potential work capacity is the bicycle ergometer. There is an important difference between the measurements made on a bicycle ergometer and those that are made on a treadmill. The difference is in the neighborhood of 10 percent in terms of maximum aerobic capacity. When an investigator studies an individual using either a bicycle or a treadmill, he must take this into account. Furthermore, the position of the individual on the bicycle, whether he is in the upright position, or whether he is in a supine position, makes a further difference in his aerobic capacity.

The question that arises here is, how are we going to determine whether or not an individual should perform a fixed load of work, namely, something like, say, 300 K cals per hour, or whether he should do work on the basis of a percentage of his capacity? One of the major factors that influences man's ability to perform is his age. As he gets older, past about 18 or 19 years of age, he generally shows a relative decline in his capacity to perform work. Therefore, if you utilize only a fixed workload, this may represent a considerable variation of the subject's capacity to do work. Consequently, it is almost necessary to measure the maximum aerobic capacity of the individual, so that you can relate the individual's performance under any stress in terms of percentage of his maximum aerobic capacity. Maximum aerobic capacity is influenced not only by age, but by the sex of the individual.

Besides characterizing an individual by the percent of his capacity to perform work, and in terms of absolute fixed load, an individual can also be studied in another way, namely, in terms of a fixed ventilation. Some of the studies that we have done have utilized this characterization. A test of fixed ventilation is easily automated and very easily conducted under careful conditions.

Body Fat

Further characterization of the individual is necessary, and one of the things that we have found extremely important is to have some measurements of the subject's body fat, so that we can determine the lean body mass or the effect of protoplasmic mass. There are two basic techniques that are commonly employed to measure body fat. One is to measure the skin folds at various places—this is not the best technique, although it is probably utilized much more than any other. A much better technique is where you measure the individual under water. This technique utilizes some of the advances in technology. Instead of measuring the individual with an autopsy scale, we use load cells or string gauges to make these measurements. Individuals vary in body fat to a great extent, and some of the effects on the individual by pollutants are determined by the amount of body fat.

We also utilize another type of technique, which is to measure people under water while they are exposed to various pollutants.

This is a new way of looking at individuals, and it is a fairly well automated technique.

Blood Constituents

Another factor in characterizing individuals, especially in terms of the effects on the individual, is blood constituents. This is a characterization that has been ignored for a long time. There has been a great deal of difficulty in some of the measurements that have been reported; namely, blood samples have been taken at unspecified times, and the measurements have been uncontrolled in terms of position of the subject. Nevertheless, blood constituents are an important factor in characterizing research subjects, in that this characterization takes advantage of the fact that we know there are changes in plasma volumes, and that these will result in marked changes in the concentration of materials in the plasma, as a consequence of the subject being in different positions.

NON-INVASIVE METHODOLOGY

I would like to discuss more methodology techniques, starting off with measures of indirect methods of measuring cardiac output. There are a number of methods available; some are practical, and some are impractical. In general, we want to get away from the invasive techniques, which we use so commonly, and go over to non-invasive techniques.

Of the non-invasive techniques, there are three that are potentially usable. One is the gas technique: the carbon dioxide re-breathing procedure, the nitrous oxide procedure, and the acetylene procedure. These are three fairly decent procedures, but they have some limitations due to the fact that they cannot be repeated at too frequent intervals.

Another approach to measuring cardiac output, which has a certain amount of value, that we have been utilizing to a great extent is the use of the impedance device. This method is—like all of these methods—not really as good as it should be in characterizing the resting individual, but it is extraordinarily comparable to direct methods, that is, the dilution techniques, if you use it in the individual who is active to any degree whatsoever. Unfortunately, this technique, although it is completely automated, can only be employed in individuals performing a slight activity, and only on the bicycle. The advantage of this technique is that you can leave the measuring devices on the individual for long periods of time. Thus, this technique detects rather striking changes that occur in the individual during the night. So, this is a fairly effective technique for measuring cardiac output over long periods of time, with the least amount of interference to the subject.

We have also tried using the echocardiogram to measure cardiac output. The only difficulty with the echocardiogram at the present time is the need for good microprocessing elements, and more importantly, the need to be able to apply the test to an exercising subject. So far, we have not had too much success using the echocardiogram on exercising subjects, but I anticipate that very shortly we will have a device that will be very effective in this regard.

Another indirect method of measuring cardiac output is to look at another part of the cardiovascular system, and that is, to measure the peripheral blood flow, whether you do it in the forearm, the lower leg, or in the finger. This is a completely automated technique over which neither the investigator nor the subject has any control. It is all automated, and can be timed. Instead of having to look at the old-fashioned records to derive the slope, the slope is derived electronically, and then the only calculation that has to be made is dividing the slope by a volume, which is also displayed automatically on the unit. The data are also put on a graph at the same time.

This automated technique is a very new development in terms of measuring peripheral blood flow. It eliminates almost all experimenter bias, and it is a very rapid procedure. In fact, you can do something in the neighborhood of 40 to 50 blood flows in a period of several minutes without any real difficulty to the subject.

Investigators are faced with several path problems when they put subjects in an environment of 48°C. Test results indicate that people of different racial origins and different ethnic origins have a different response to exposure to a hot environment. Any time one studies subjects, one must characterize the subject not only in terms of his physical and medical characteristics, but in terms of ethnic origin, at least to some extent.

A newer development has involved an examination of nasal airway resistance. We are now working with a device to measure both nasal airway resistance and oral airway resistance. This is an important new development, since it provides for separation of two portions of the respiratory system which have not been looked at too carefully in the past, and that is the point of time when the individual shifts from breathing through his mouth to breathing through his nose, or when there is a combined effect of those two functions. Microprocessors handle the calculations and the evaluations, and determine the pattern of the experiment.

Another factor that I think is of some importance is the need to develop devices that telemeter the heart rate. We measured a cross-country coach, and every time he saw any of his runners come by, his heart rate went up to 160, yet he gave the appearance of having no reaction to the race. Similarly, we measured the heart rate of a volleyball coach. His team lost the first set, won the next four, and despite the fact that during the entire period of time he sat very quietly, and apparently was unconcerned about the entire event, his heart rates went as high as 160. I might point out that his maximal heart rate was 180, so in that he is in a maximal aerobic capacity test, he is under considerable stress. These studies indicate that many of the studies that we have been doing on subjects where we look at them and obtain measurements of the heart rate or using the electrocardiogram only at the fixed intervals may be missing a great deal.

A few devices have been developed to make it possible to look at individuals non-invasively, and at the same time, to describe very simply the way in which a subject can be categorized by utilizing, again, non-invasive techniques. The more effectively you can analyze the subject's response and his condition, the more effectively you can determine what is happening to the individual.

One of the main advantages of the new methodology is not simply that researchers are able to utilize computer devices or new developments in electronics to help build better instrumentation and to help organize the exposure of the individual, that is, to determine what he is going to respond to and how he is going to respond to it. More importantly, the new methodology has provided us with a means by which we can take the other techniques that are not usually available to us, from the standpoint of our own expertise, but which are commonly used in other areas, and by proper handling and working with electronics people, and with people who are interested in physiological response, it is possible to develop new devices that will make it easier for us to successfully invade the individual without doing it by an invasive technique.

Discussion Summary

Participants discussed the merits of using microprocessors rather than minicomputers in research activities. Discussants said that the minicomputers are more likely to break down than the microprocessors, but the microprocessors are more adept at carrying out different operations simultaneously. Some laboratories use minicomputers as a supplement to the microprocessors.

Discussants observed that the use of microprocessors has enabled investigators to automate the measurement of various bodily functions. In one participant's laboratory, the data that is obtained is tape-recorded to the IBM systems where it is analyzed. Tape-recording of data is an easy process, and the eight-channel capability enables the investigator to collect a good quantity of data.

It was noted that although the development of automated analytical procedures can be a timely and expensive process, these disadvantages are offset by the tremendous amount of time the investigator saves in the long run once the automated units are set up.

Participants discussed the steps the accumulated data goes through to be put into an analytic form. The automated units have a data base for each research subject that includes every measurement made on the subject. Statistical analyses are made from this data. The computer can immediately produce data on the basic body functions. To obtain derived functions, the base material is put on a data base, and then the various derived functions of statistical analysis of the computer data are carried out on the computer from the data base. Discussants noted that it is important to develop a data base that can be manipulated to handle large volumes of data.

In a discussion of the differences between the Bruce system and the Balke technique, participants said that the Balke technique is more suited to studying populations of different ages than the Bruce system. For example, the Bruce system cannot be used to study children under six or seven years of age, or on adults in their seventies and eighties.

The Bruce system is used in some laboratories, but not for normal populations because there is no way of characterizing subjects throughout their entire life span or in relation to their sex.

Participants also talked about the various methods of measuring blood pressure. Measuring blood flow by using radioisotopes is a viable technique, but it is invasive. An alternative is to use strain gauges to measure peripheral blood flow. Discussants said that attempts to automate the measurement of blood pressure have been unsuccessful, and that the best measurement is to use a blood pressure cuff and two good ears.

Rationale for Experimental Design

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I would like to describe how we decide what clinical environmental research we are going to conduct within the constraints imposed by ethics, the law, and logic. I think it is very important, in discussing the rationale of experimental design, to bear in mind a few definitions and a few relationships.

CLINICAL ENVIRONMENTAL RESEARCH: A DEFINITION

Over the years that I have been involved in this type of activity, I have developed a simplistic definition of clinical environmental research. I think, as we expand our purview and bring new tools to bear on the topic, and as we learn a little more about the problems of environmental medicine, my simplistic definition will merit some scrutiny, and perhaps, need to be overhauled and expanded. But very briefly, the definition I have used is that any time you manipulate a human being and his environment, you are doing clinical and environmental research. Now, what does that mean? More germanely, what doesn't it mean? When we study what is happening to a population under specific circumstances, or when we simply avail ourselves of the opportunity to study a population, I do not consider that we are conducting clinical research.

I think some might argue with that, so I will give an example of what I am talking about, that is, what we have been doing in Chapel Hill all along, and what most of our colleagues have been doing around the country. In clinical environmental research, the subject and his environment are manipulated. The subject is placed in an artifically-controlled environmental laboratory. You manipulate that person by putting him on a bicycle ergometer, on a treadmill, or by having him breathe through a pneumotachometer or into a spirometer, or in some other way study some aspect of his physiology. You do not allow the subject to range normally through his environment. Then you manipulate in a positive, very carefully thought out and contrived way, the subject's environment. You manipulate the environment by making it clean to a standard condition, putting the subject in a Class 1,000 or a Class 100 clean room, and the investigator gets a baseline of information.

The investigator may manipulate the environment by having the subject breathe an air pollutant, or by manipulating the temperature, relative humidity, light intensity, sound levels, isolation, or other characteristics of the environment. This is the simplistic definition of clinical environmental research. I think, though, as we familiarize ourselves with the rapidly, exponentially growing technology that is available to us, we will need to enlarge that definition.

Going back to one of the historical antecedents of clinical environmental research, one of the projects of the Harvard Fatigue Lab was to study the adaptation of workers to their new environment as they constructed what was then called Boulder Dam. That project was certainly a form of clinical environmental research. Clinical research was done on these workers as they adapted to the new environment, but their environment was not manipulated. The subjects were manipulated only to the extent that some measurements were made concerning their adaptation.

As we face the newer, more challenging, and more far-reaching questions that society will put to us with respect to our environment, we will need to adopt a broader definition of clinical environmental research. For the most part, though, my discussion of the rationale involved in design experiments in clinical environmental research is based on the simplistic definition, where you put a person in a controlled environmental laboratory, and manipulate his environment in a predetermined, well-thought-out way.

RELEVANCE: A KEY TO EXPERIMENTAL DESIGN

The theme of my discussion is relevance. We are designing experiments and studies that have a very specific relevance to a question posed by society. Frequently, in other kinds of clinical research, much activity is pursued in a somewhat descriptive way. By that I mean that we are not really focusing before we undertake the research, or before we design a particular study on a very precise question. We are exploring the results of a particular intervention, be it surgical or medical, and we do not have all of the consequences of that intervention completely in mind.

The objectives, then, put in this simplistic paradigm of clinical environmental research, are to focus on a specific question that society is posing, and then to establish the experimental framework within which to address that question. If we do not keep these objectives in mind, we will conduct much clinical environmental research that will not be relevant to the questions that are being asked.

I think we do need to keep in mind the relationship between clinical research, human experimentation, and probably, the other couple of ways that we can get at the answers to the same questions. Much of the information that precedes the clinical experimentation, and much of the information that is the basis for the rationale of the experimental design, comes from two other disciplines--basic toxicology and epidemiology.

Basic toxicology has to precede and continue to be an integral part of the rationale for clinical experimentation. The amount of basic animal toxicology that we have at our disposal to design clinical research will have a profound effect on what research is done and how it is done, and of course, on the rationale for approaching a particular experimental design.

The discipline that I would like to discuss is epidemiology. Most people think that epidemiology is not really a discipline, that it is a state of mind with which you approach a problem. But epidemiology is important because it is closely related to clinical research, and it deals with the species of interest, human beings.

Epidemiology differs from clinical research in that it lacks two of the overriding characteristics included in the definition of clinical research. In epidemiology the subject is not manipulated. As a matter of fact, in epidemiology you do everything you can to avoid interfering with the normal behavior of your subject. Epidemiologists are concerned about a kind of Heisenberg's principle of biology: anything you do to study your subjects in an epidemiologic study design will interfere with those measurements because you specifically do not want to intrude on your subjects' way of life, and you certainly do not want to manipulate their environment.

I want to discuss briefly the interrelationship between epidemiology, clinical environmental research, and environmental toxicology. In the latter discipline, we have an exquisite handle on the dose, and you can do anything you wish to the subjects because they are expendable, and they are available in large quantities of inbred strains. You get all kinds of very precious, very specific information from these animals, but we always have to deal with the problem of extrapolating from these non-human species to what is going on in people. We know that there is often a great leap in extrapolating from animal data to the human situation.

In epidemiology, we take advantage of the fact that we are studying humans, but we have only an imperfect idea of what the dose or what the extent of environmental stress is. There are just a few parameters that we can measure, and most of them with less than satisfactory precision.

Taken together all three disciplines give us the coherent database from which we move toward regulatory action. With these interrelationships and strengths and weaknesses of the various approaches in mind, I would like to focus more on the discussion of the rationale of designing human experimentation to study the effects of environmental agents.

LOGISTICS CONSTRAINTS

I think it is important and absolutely necessary to take into consideration logistic constraints. I have to face the fact that I have only three sets of resources to work with: people, money, and time. I cannot control the third resource, but given the objective that targeted research has to be relevant to social questions, you must decide how to go about choosing the right question and answering that question with the resources at hand. A laboratory may require $10,000 a day to operate. You have a through-put of so many human subjects in a reasonable experimental paradigm per unit of time, so you have to very carefully decide how to use these scarce resources to address the question you are trying to answer.

That is an integral part of the rationale of experimental design. I could come up with many experimental designs that would be appropriate, that would be scientifically meritorious, that would supply answers to the questions in an intellectually satisfying way. But we do not have the luxury of pursuing research questions in that particular way. We have to look at the end points, the criteria for subject selection, to make certain that when we begin a five-day study that all of the subjects will participate for five full days, because the data each day are really quite expensive. These elements in the rationale of the study design are more important than we scientists like to admit. In developing a rationale for an experimental design, it is important to have a statistical design that is highly parsimonious.

I will give an example that will illustrate several points with respect to subject selection, range of susceptibility, and a few other points. The best example I can give is one having to do with carbon monoxide research because it is very simple.

The carbon monoxide experiment was based on what we knew we could do, in view of some of the material constraints. It was based on what we knew carbon monoxide should do to people, and on the fact that we had an ambient air quality standard for carbon monoxide that was rather low. The automotive industry said the standard was irrationally low, but there was no real basis for their statement.

I discussed with a colleague what test he thought we ought to conduct to study the effect of carbon monoxide on a particular human function. Historically the effects of carbon monoxide on the central nervous system had been the focus of research. My colleague was a cardiologist who knew about exercise stress testing and exercise electrocardiology. He said that the myocardium does not function very well during relative hypoxia. As a matter of fact, the blood leaving the myocardium has a partial pressure of oxygen, a PO_2 of 25 millimeters of mercury, which is as low as it ever gets at rest. It does not get any lower at exercise. So, if you do something to interfere with oxygen delivery to the myocardium, you almost expect a priori to be able to measure some effect. We could measure something going on in the myocardium at relatively low levels of carbon monoxide. Here is how we did the experiment. We had people get on a treadmill and do an exercise ECG before they were subjected to a standard dose of carbon monoxide. One of the nice things about this test is that we can measure carboxyhemoglobin in the circulating blood, so we have an accurate estimate of the body burden of this environmental agent. We do not even have to depend on ambient air measurements, we just measure carboxyhemoglobin in the blood. We gave the subjects a certain amount of carbon monoxide to breathe, and we measured the carboxyhemoglobin again, and then we had them go on the treadmill again, and we looked at the electrocardiogram.

In young, healthy adult males, who were the least susceptible because they should have the healthiest myocardium, we did not see any changes in the electrocardiogram. We saw changes in heart rate at various levels of activity. There was a price paid for the carbon monoxide load, but it did not show up in that particular objective parameter when we looked at the electrocardiogram.

Then we postulated that a cohort of men whose mean age was 45 instead of 20 should include a few individuals who had preclinical ischemic heart disease, and that they should show some changes during the same experimental design. We tested that hypothesis and found that our presumption was true, that there were a certain number that changed their Minnesota code during the course of the experiment. We postulated that if this were true, then people who have well-defined, stable angina pectoris, people who have well-characterized coronary artery disease, ought to be much more sensitive to carbon monoxide. We tested that hypothesis, and it was valid. This is an oversimplified presentation of this particular set of experiments, but it serves as an example of logical progression of hypothesis testing with the results of each experiment influencing the design of the subsequent one.

HISTORICAL ANTECEDENTS OF CLINICAL RESEARCH

Clinical research has been around for a long time in one form or another, only recently have scientists in general, not just physicians, begun to focus on man's relationship to his environment. I believe that the Harvard Fatigue Lab of the mid-1920's represents the keystone of clinical environmental research. The Harvard Fatigue Lab was housed in the Harvard School of Business because the people who were interested in setting up the lab wanted to investigate "the adaptation of the normal individual to industry."

There was a certain amount of social responsibility in industry at that time, and, as I read it, a hard-nosed desire to find out how you could maximize human productivity under certain environmental conditions, i.e., industrial conditions.

The techniques, the attitude, and the rationale for environmental human clinical research were established by the investigators in the Harvard Fatigue Lab around 1927. The 20-year life of that institution takes us just past World War II. Interestingly enough, many of the alumni of the Harvard Fatigue Lab are active in clinical environmental research today. They moved on during the course of World War II to broaden their perspectives, and have led into what we have been doing for the last decade in clinical environmental research. These investigators became involved in cold and heat stress experimentation because of military operations under those conditions. Of course, the human element was the salient element of all that research--altitude physiology, dividing physiology, and submarine physiology, as examples.

A modern corollary of that research is now being conducted in the hyperbaric chamber at Duke University. Because of the quest for new energy sources, investigators are studying ways man can adapt to 1,000 feet of sea water so that oil may be extracted from the North Sea and other places.

We are not alone in developing a rationale for clinical environmental research. We can rely on a number of years of high-level investigator or research scientist history to help us develop the rationale for clinical environmental research.

FURTHER CONSIDERATIONS IN DEVELOPING A RATIONALE

We must consider three further characteristics when developing our design rationale. The first characteristic is subject selection. What is the rationale of subject selection? Perhaps because most of my earlier research work was with animals, I regret not being able to deal with nice inbred strains of mice when I am conducting human experimentation. Because of that, I suppose, I sometimes err in the direction of trying to design clinical experiments where I have a very homogenous population. I try to control as many of the covariants within the population as I possibly can, to minimize both inter- and intra-subject variance.

The globe is not populated with 20-year-old robust Caucasian males who happen to be students at the University of North Carolina. Many inter-subject characteristics must be taken into consideration--ethnicity, race, and geography, to name a few. There are differences in cardiovascular performance and pulmonary performance, and there are probably profound differences in metabolic characteristics that we are just now learning to measure. What is true for our experimental subjects may not be quite true for the population at large. However, I think tests have to be based on a highly homogeneous population so as to minimize the inter-subject variance.

My tendency as a first step is to try to identify all of the characteristics I can possibly measure in the subjects, and specifically select for or against those characteristics. In this way, I achieve as homogeneous a population as possible, albeit an artifical one. Using the information from the first step, I inject that information into the rationale for the succeeding experiments that we do, changing the characteristics of subject selection as I pointed out in the carbon monoxide experiments.

The second characteristic to consider in developing a rationale is dose selection. Dose in the usual sense of the word is the amount or level of environmental stress, or the quantification of the environmental agent that will be used in the experiment. There is a bit of circular logic involved in how you decide what is going to happen with respect to your dose selection. At the minimum, we like to make some statistical statements about dose selection and relevance because we are conducting the research for a specific reason.

The third characteristic that must be considered in developing a rationale for clinical experimentation is the selection of end points. As I indicated earlier, a cardiologist will not worry about evoked potentials, and a neurophysiologist does not care much about stroke volume. The person who designs research in clinical environmental medicine has to take several backward steps to look at what is known about the biology of the environmental agents he is studying. He must design experiments that are constrained by staff and budget, and take advantage of an exposure situation to explore a variety of end points that are judged to be the most relevant biologically, and the most likely to yield important information.

In summary, the rationale for designing clinical environmental research is multifaceted, and has to do with research objectives and available resources. Most importantly, because both the objectives for the research and the resources that are available are determined by the questions that society asks, the rationale has to strive diligently to maintain a high degree of relevance to the social questions that are being posed.

Discussion Summary

The issue was raised whether experimental scientists should concentrate on anticipating and solving problems, rather than waiting for problems to come up and then solving them. Participants noted that some scientists currently operate according to the former procedure. For example, scientists have been successful in using biomathematical engineering to study the possible effects of certain pollutants.

However, investigators said that they do not always have the resources to design and conduct what would be considered anticipatory studies. In addition, many of the topics chosen for study are questions that are formally posed to the EPA by Congress and that are important to the public (e.g., how safe is our environment?) Thus, the investigator has a limited amount of time in which to conduct anticipatory studies.

Participants also discussed the drawbacks in conducting experiments in a clinical rather than a natural setting. Is a clinically manipulated environment representative of what goes on in the natural environment? Discussants considered the case where a group of factory women who, in a laboratory situation sweat less than men, were observed on the job to be producing as much sweat per hour as the males did in the clinical setting. Although this points up the fact that the way a subject reacts in the laboratory may not be the way he reacts in a natural environment, participants pointed out that no matter what group of subjects you are working with, the investigator will always be faced with some form of bias. For example, the factory women who disproved the theory based on clinical research that women sweat less than men, in themselves are not representative of women in general. They are women who have chosen to work in a hot factory, who have chosen to participate in the study, and so forth. Thus, any test reactions, be they derived from a clinical or natural setting, are not necessarily representative of what occurs in the general population.

Finally, investigators discussed the need to allot adequate time to completely examine and answer a study question. Participants felt that the Congress and EPA administrators appreciate the need to plan long-range targeted research, and that money may be set aside for anticipatory research. Anticipatory research is not research that investigators plan to conduct in the future; rather, it is research that will take many years to complete.

Subject Selection, Investigator Interactions, Informed Consent in Clinical and Environmental Research

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> A revolution is going on in psychology. A different image of man is being tried as a guide to research, theory, and application. Over the years, theorists have conceptualized man as a machine; as an organism comparable to rats, pigeons, and monkeys; as a communication system; as an hydraulic system; as a servomechanism; as a computer--in short, he has been viewed by psychologists as an analogue of *everything but what he is*: a person. Man is, indeed, like all those things; but first of all he is a free, intentional subject.[1]
>
> --Sidney M. Jourard

PHILOSOPHICAL PERSPECTIVES: BEHAVIORISM vs. HUMANISM

During the past two decades a lively debate has ensued between the proponents of the humanistic and the behavioristic traditions in psychology and related disciplines in the social and clinical sciences. This debate is directly relevant to the conduct of human research, since many time-honored principles concerning the relationship of the subject and experimenter have been called in question.

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Beneath the "sound and fury" of men like Sidney Jourard and B.F. Skinner lies the fundamental philosophical question of man's freedom to behave in a non-deterministic, unpredictable manner. According to a strict behavioristic model (or Freudian model for that matter), man's behavior is entirely determined by either external environmental stimuli or unconscious inner motives and drives bubbling up from the depths of the psyche. Although Skinner and Freud may seem to be rather incompatible bedfellows, Skinnerian and Freudian theories are both highly deterministic with respect to human behavior: that is, both theories imply that human behavior can be predicted and, to some extent, controlled by the appropriate manipulation of internal or external stimulus conditions.

This deterministic view of man conflicts rather strenuously with the traditional humanistic view of man as a rational being, possessed of a variety of constitutional freedoms, including the right to withdraw from any scientific investigation whenever the spirit moves. In fact, the humanistic revolution in social psychology has spawned an entire field of research devoted to subject-investigator interactions.[2,3] The implications of the humanistic revolution extend far beyond psychology, however, since the Federal Government has now imposed strict regulations in accordance with the National Research Act to safeguard the "free will" or voluntary nature of participation in all HEW-funded human research projects.[4] In essence, these legal and ethical constraints are designed to preserve the freedoms essential to the humanist view and to deny the behavioral controls alleged to the opposing view.

Requirements of the National Research Act are difficult, in some respects, to reconcile with scientific objectivity, as well as specific objectives of environmental research. Miller[5] has succintly summarized the dilemma: "The goals of meaningful scientific inquiry may be at odds with the value of treating man in a dignified and respectful manner." This paper will explore some of the potential conflicts among the elements of informed consent and the conduct of environment research.

The traditional objective of human research is to determine the effect of some carefully controlled manipulation on behavior. In other words, we predict that some external stimulus (such as noise) or internal stimulus (such as food or drugs) will alter behavior in a systematic way. If we seriously entertain the notion that man behaves in a totally non-deterministic, unpredictable manner, then human research would be a waste of time. We can easily extract ourselves from this paradox by adopting a compromise philosophy wherein some behaviors are subject to external control, while other behaviors are mediated by internal volitional processes. Even the most extreme humanist would be unlikely to deny the effects on human behavior of heat, cold, sleep deprivation, or carbon monoxide poisoning.

What is the consequence of man's tendency to behave unpredictably? The exercise of free will in the laboratory yields considerable noise in the data which the humanist calls "individual differences" and the behaviorist calls "intersubject variability." At this point the two investigators rapidly part company, for the humanist is concerned with *enhancing* individual differences, while the behaviorist seeks to *minimize* intersubject variability. The manner in which subjects are selected determines, to a large extent, how much heterogeneity or homogeneity the investigator may expect. After a decade of behavioral research, however, we can attest that the application of stringent criteria based on standard personality and medical inventories, physicals, and interviews to secure "normal, healthy" populations has been remarkably unsuccessful in reducing intersubject variability. No matter how rigorously subjects are screened in preparation for human experiments, there is little hope of ever attaining a pure laboratory strain of *Homo sapiens*!

The problem of intersubject variability is particularly severe in clinical environmental research where the objective is to define the *threshold* level at which a given substance produces *significant impairment* in function. Threshold effects, by definition, are "just noticeable differences." The challenge in this field is to minimize individual differences, regardless of the philosophical bias of the investigator.

SELECTION OF A PROTOTYPE SUBJECT

How do we go about selecting human subjects for environmental health effects studies? Subject recruitment, though seldom pursued as an independent profession, has evolved to an exacting science in Chapel Hill. Since the University constitutes the primary industry, the student population is the major, if somewhat transient, source of subjects. That is, the normal, healthy, red-blooded collegian represents our closest approximation to a standardized laboratory animal.

One might object at this point that our choice of "prototype man" is not particularly representative of the larger population to whom we wish to generalize our findings. Dr. Shy, for instance, argued at this symposium for the use of specific clinical populations considered to be unusually sensitive or susceptible to certain environmental insults. The rationale for using healthy young adults is that any functional impairments observed can be inferred to be more severe in susceptible populations. The probability of observing effects attributable to low level exposure may be artificially low in healthy young adults leading to Type II errors of statistical interpretation. That is, we may conclude that substance "X" produces no deleterious effects in the general population when, in fact, the same exposure may actually produce a functional impairment in an older or less healthy population. The risk factor, however, is correspondingly lower in healthy young adults than other populations.

How do we define our standard subject? Prior to initiating any experiment, the principal investigator provides the recruitment staff with a specific list of criteria. I will quickly review the criteria used in selecting subjects for recent neurobehavioral and physiological studies of environmental insult. In general, the criteria for selection of subjects to participate in studies which involve at least a marginal health risk are considerably more stringent than the criteria used in other studies which do not entail any health risk. The monetary inducements also vary relative to the associated risks or discomforts such as repeated blood draws.

Ethical considerations preclude the exposure to risk of children, minors, or any other population that cannot provide informed consent. Current studies are limited to adults aged 18-40, although middle-aged and elderly subjects have been used in previous studies of the effects of CO on the onset of angina pectoris.[6]

For pragmatic reasons, we have limited research to adult males. The potential danger of toxicant effects on the unborn fetus and the increased variability associated with hormonal changes during the menstrual cycle are primary considerations. In order to preclude the possibility of fetal damage, women must be given a pregnancy test prior to each experimental session. Since the observed effects of environmental toxicants, particularly at low concentrations, tend to be extremely subtle, the physiological and psychological state of subjects must be maintained as constant as possible. Exposures would have to be carefully synchronized to specific times in the menstrual cycle of women subjects to control for hormonal variation. These problems are avoided by restricting experiments to males.

This strategy can be problematic in the present climate of sexual equality. For example, three coeds once walked into our laboratory demanding equal time and equal pay. An ozone experiment was then in progress in a transparent plastic exposure chamber. The girls were invited to observe a subject who was pedaling a bicycle ergometer while stripped to the waist for ECG recording. When the girls were asked if they still wished to participate, two blushed and withdrew their request. The third coed, however, smiled and asked when she could begin. The Institutional Review Committee, however, had not authorized us to expose females to ozone!

The variable of race, like sex, raises ethical and pragmatic difficulties. Ewing et al.,[7] for instance, have shown that blacks, orientals, and whites are differentially tolerant to the effects of alcohol. There is reason, therefore, to expect differential racial responsivity to environmental stressors such as carbon monoxide which is also considered to be a CNS depressant. If a multi-racial population is studied, a sufficiently large sample from each racial group is required to statistically evaluate possible racial differences. The usual practice (which could easily be construed as discriminatory) is to use subjects of a single race in order to eliminate this source of variability from the data. One strategy to avoid statistical and ethical conflicts is to restrict subjects in an individual study to a single race, but to use different races in different studies.

How do we define "psychological" normality? Prospective subjects complete the Minnesota Multiphasic Personality Inventory (MMPI) and must score below the 75th percentile, unless otherwise specified by the principal investigator, in order to participate in environmental studies. Scores on the MF scale are disregarded, since most college students score high on this scale. The MF scale reflects aesthetic interests more than the masculinity-feminity dimension for which it was originally intended.

The use of the MMPI as a psychological screen is admittedly arbitrary, although the test is standarized and widely used. The MMPI is neither foolproof nor all inclusive. For instance, the standardized MMPI profile does not indicate if a prospective subject is claustrophobic. It is simpler to ask directly if the individual is afraid of staying in a closed room for a long time.

Why should the environmental researcher be concerned about the psychological normality of prospective subjects? The need is readily apparent for physical examinations and careful scrutiny of the medical history of prospective subjects to minimize the possiblity of extreme physiological reactions to pollutant exposure. It is also necessary to assess the emotional stability of prospective subjects since prolonged confinement in a relatively small testing chamber and/or exposure to a substance that is presumed to have at least mildly toxic effects can induce considerable psychological or emotional stress, even in psychologically normal subjects. Individuals exhibiting any signs or history of psychological abnormality should not be used in environmental health effects studies.

The potential psychological risks inherent in any clinical environmental study are seldom considered seriously by investigators and are rarely articulated to subjects during pre-experiment briefings. In many studies, this oversight represents a clear breech of informed consent! The measurement of pollutant effects on psychological dimensions such as mood, anxiety, or hostility has likewise been neglected and constitutes an important area for future study in clinical environmental research.

Smokers have been excluded from experiments testing the effects of carbon monoxide, ozone, and sulfuric acid aerosol. This exclusion is particularly important where the test substance is expected to alter oxygen uptake or respiratory function. How long should prospective subjects have been non-smokers in order to ensure "normal" lung function? Our physicians have specified a minimum of 10 years in oxidant experiments, a requirement that has strained the resources of the recruitment staff on occasion. In essence, this requirement limits subjects in college-aged populations to those who have never smoked tobacco.

Should the same criteria apply to marijuana smokers? In practice, a double standard is applied in the case of "pot" verus "tobacco" smoking. Investigators have adopted a much more tolerant attitude toward the occasional marijuana smoker than to the occasional tobacco smoker. At least half of our undegraduate recruits admit to the occasional use of pot, and the percentage is probably much higher. Why the double standard? In this case, scientific objectivity has been sacrificed to humanistic (and pragmatic) considerations.

Other criteria used in subject selection include limitations on the use of stimulant beverages. Subjects should not have consumed more than two cups of coffee, tea, or coca-cola, or any other liquid stimulant within one hour of the start of the experiment. In addition, subjects cannot have consumed more than the following limits of alcohol within the 24 hours preceding the experiment (these limits vary for different experiments): in neuro-physiological experiments, the limit is 24 ounces of beer, or approximately two cans, within 24 hours of the test; 12 ounces of wine, or approximately two glasses; three ounces of hard liquor, two shots of whiskey, rum, or vodka, and so on.

Furthermore, the subject cannot take any drugs, prescribed or otherwise, within 48 hours of the experiment. The term "drug" includes antibiotics, antihistamines, barbiturates, amphetamines, marijuana, heroin, cocaine, steroids, or other substances prescribed or self-administered for health, happiness, or habit. In some cases, the attending physician or psychologist may allow the subject to take aspirin, bufferin, or related compounds before the experiment.

To avoid the problems of sleep deprivation or the converse during the experiment, subjects are required to have six to ten hours sleep during the previous night, and to sleep regularly within this normal range over the course of the experiment.

Prior to exposure to any toxicants, prospective subjects complete an exhaustive medical history, the Duke Medical Inventory, and are given a physical exam by EPA physicians. Any history of allergies or significant medical problems generally excludes candidates from participating in an experiment.

Does the stringent selection process destine our experiments to produce negative findings or no effects? Perhaps it does. In other environmental laboratories in this county and in Europe there is much feeling that an investigator would get better results if he used a susceptible population.

INVESTIGATOR ATTRIBUTES AND INTERACTIONS

We have focussed thus far on attributes of prospective subjects which might influence performance in an environmental health effects study. Attributes of the experimenter can likewise affect the performance of subjects and possibly bias experimental results. This problem has been studied intensively by social psychologists during the past decade. Rosenthal[1] reviews a wide range of biological (e.g., sex, age, race) and psychosocial (e.g., anxiety, hostility-warmth, authoritarianism) attributes of the experimenter which affect subject behavior. For instance, college-aged subjects tend to cooperate better with experimenters of their own age and race, but of the opposite sex. The simple effects of biological variables, however, can be counterbalanced by or interact with a multitude of psychosocial variables. An experimenter perceived to be anxious, hostile, or rigidly authoritarian will elicit less cooperation from subjects than an experimenter perceived to be confident, warm, or tolerant.

These observations may seem banal, but researchers seldom consider such obvious subject-experimenter interactive effects in the design of a study or the analysis of data. Let us consider a hypothetical example. The objective of a proposed study is to determine the effect of low level oxidant exposure on treadmill endurance in healthy young adult males. Experimenter A is an attractive, congenial young woman, and experimenter B is a quiet, slightly over-weight, middle-aged man. Which experimenter is likely to achieve better rapport with subjects? And how might subject-experimenter interactions affect the results of the study?

Based on age and sex factors, we can predict that subjects will probably establish better rapport with the female than with the male experimenter. In terms of performance, we can also predict that subjects will probably exhibit greater treadmill endurance for the female than male experimenter. The objective of the experiment, however, is not to enhance subject-experimenter rapport or treadmill performance, but to impartially determine the effect of oxidant exposure on treadmill endurance. If we wish to minimize the effects of experimenter attributes on performance, we would probably obtain less biased results from the middle-aged male!

This example, furthermore, confronts us with a basic dilemma in clinical environmental research. Subject-experimenter interaction is but one of many motivational variables which can affect the performance of subjects. Since the effects of low level toxicant exposure are likely to be subtle, motivational variables of this kind can easily mask the effect of exposure and lead to false negative results. On the other hand, the current Zeitgeist of human research, mandated in many respects now by federal regulations, is to treat subjects in a warm, open, humanistic manner. Subjects are persons, not guinea pigs! The challenge is to strike a balance between humanistic concerns and scientific objectivity!

SUBJECT EXPECTANCIES, INFORMED CONSENT, AND SCIENTIFIC OBJECTIVITY

I would like to explore one final aspect of subject-investigator interaction that is known to have considerable effect on subject performance. What a subject expects to do or to happen in an experiment is an important determinant of his behavior in that experiment. Psychologists frequently refer to the expectancy variable as experimental or instructional "set." Physicians are familiar with this phenomenon as the "placebo effect."

Appropriate control conditions must be included in experiments to differentiate expectancy effects from the effects of other variables that the experiment is designed to test. Drug studies, for instance, usually include a placebo condition in which subjects unknowingly receive a substance that does not contain the active ingredients of the drug being tested. Subjects receiving the "placebo" are deceived by the investigator in order to distinguish the genuine effects of drug "X" from the spurious, but often therapeutic, effects of subject expectancy.

Expectancy effects can be controlled or minimized by other means. A method frequently used in the past was simply to conceal from subjects the true objectives of the study or the hypotheses under test. Although the necessity for placebo conditions in drug studies is generally accepted, the use of deceptive procedures in other types of human research is rarely sanctioned any longer by institutional review boards. Full disclosure to subjects of the objectives, procedures, discomforts, and risks constitute elements of informed consent which must now be obtained prior to participation in any experiment.

We are faced again with a dilemma in which ethical considerations and human rights may be at odds with scientific objectivity. *A priori* disclosure to subjects of the anticipated effects of an experimental manipulation will obviously shape expectancies and bias responses. Let's consider a specific example: an experimenter warns subjects that ozone exposure may cause temporary irritation of the eyes, throat, and chest; headache; and nausea. The experimenter cannot obtain a valid, unbiased measure of the frequency or severity of these symptoms following exposure. Nor can single- or double-blind control procedures be effectively employed since the presence of ozone is readily apparent to both subject and investigator.

THE ELEMENT OF RISK IN CLINICAL ENVIRONMENTAL RESEARCH

Specification of risk in environmental research also raises contradictions. How can we adequately inform subjects of the anticipated risks of exposure when one of the basic objectives of environmental health effects studies is to determine empirically what those risks are? On the other hand, we have no legal right to expose humans to any conditions that might significantly impair any vital function for an extended period of time. The margin of risk in any proposed human study must be extremely small, and any functional impairments produced by exposure must be transient and completely reversible. The enigma of clinical environmental research, therefore, is how to determine the threshold of human risk to pollutant exposure without exposing humans to significant risk!

In conclusion, federal regulations to protect the rights of human subjects severely limit the scope and conduct of clinical environmental research. The U.S. Environmental Protection Agency has been mandated by Congress to determine the risk to human health of a wide gamut of potentially toxic substances. The Department of Health, Education, and Welfare has likewise been mandated to protect the rights of human subjects. Unfortunately, the two mandates are not entirely congruent. Clinical environmental researchers must carefully tread the tightrope between these opposing mandates since the achievement of meaningful environmental quality standards hangs in the balance.

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Discussion Summary

Participants discussed the importance of physical criteria in screening subjects; for example, what is the subject's aerobic capacity? Is the subject under or overweight? It was agreed that all subjects should undergo a rigorous physical examination before being allowed to participate in an experiment. It was further noted that some investigators simplify the process of finding healthy subjects for each experiment by forming subject pools from which to draw subjects as they are needed.

Discussants also questioned how the investigator verifies the information the subject tells him. For example, how can the investigator be sure that a particular subject has never smoked a cigarette? Or that the subject didn't drink four glasses of wine the night before the experiment? Some investigators said they take subjects at their word. Others devise series of questions designed to elicit the truth from prospective subjects.

Participants discussed methods of screening middle-aged and elderly subjects. In general, the screening method depends on the purpose of the study. For example, middle-aged persons are regarded as particularly sensitive to pollutants. Therefore, any tests involving pollutants would necessitate testing to ensure that none of the middle-aged subjects are over-sensitive to pollutants.

Discussants agreed that all subjects, regardless of age, must be carefully tested, perhaps more intensively than they are at present, to ensure the subjects' safety.

Assuming that there is no such thing as a "normal" man, discussants questioned how investigators arrive at a set of criteria to select subjects for specific experiments. The process of determining a set of criteria was described as "evolutionary." Thus, over the span of a number of tests, investigators gradually develop a list of variants that have proved to be important in choosing subjects and preparing them for an experiment. For example, after conducting a number of tests, investigators determined that a lack of sleep would distort a subject's test responses. Thus, subjects are required to sleep a certain number of hours on the night before the experiment.

In some instances, criteria are tailored to specific experiments. For example, in tests involving respiratory measures, investigators would want to know whether a subject has a history of lung disorders.

Some discussants indicated that they have used female subjects in their experiments with no problems. Other participants urged the use of healthy middle-aged and elderly subjects in experiments.

Finally, one participant suggested a randomization of the double blind procedure, to avoid biasing a subject's test response by telling him at the start of the experiment what effects to expect. A subject would still know what test effects to expect, but he would not know on what day he would actually be exposed to the test substance.

Some participants felt that if a subject was sufficiently susceptible to the powers of suggestion, it would not matter whether or not he was exposed to the test substance because he would react the same in either situation. In addition, participants said that if the effect of the exposure is strong enough, responses induced by suggestion would not be critical.

Acute Versus Chronic Studies

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Acute studies are those that involve an exposure of less than 12 hours duration in a controlled environment, with observations of changes in physiological function. Recent concern over air pollution has undoubtedly precipitated an increase of interest in what these studies may reveal and also in their limitations. If my memory serves me right, in the 1890's, J.S. Haldane graphically demonstrated the unique importance and value of human studies when he breathed carbon monoxide when exercising and noted the effects on himself. I recall that the experiment ended when he fell off the bicycle ergometer. Haldane noted that these experiments gave him an insight into the physiological effects of progressive carbon monoxide intoxication, which he couldn't possibly have gained from animal observations.

I believe that a few years from now, historians will be rather surprised at how slowly the development of acute studies in a controlled environment occurred. After all, the major pollution episodes took place more than 20 years ago, and it is still possible to go into the medical literature looking for a specific answer to an important question and find that very little experimentation has been done. In the case of sulphur dioxide, for instance, we do not know precisely the range of individual variability, or the association of a high sensitivity to sulphur dioxide as measured by changes in airway resistance, to other thresholds of sensitivity as measured by the inhalation of mecholyl or histamine. We do not have a precise quantitation of the effect of mouth or nose breathing in an atmosphere of SO_2 on the development of changes in airway resistance. We do not know whether a two-hour exposure on one day will influence the response in a given individual in succeeding days. We do not know whether the acute response to sulphur dioxide is any different in individuals who live and work in relatively high concentrations of this gas and, in general, we have very little acute laboratory data to put alongside our guesses of its chronic effects. I mention these obvious outstanding questions to indicate that it should be a matter of surprise to us that one can ask these and find that we do not have reliable laboratory data to answer them, when we have known for a long time that sulphur dioxide is one of the principal constituents of the older type of air pollution episode.

ACUTE EXPOSURES

In general, we require that acute studies mimic actual exposure conditions and we try to isolate independent variables. This may be a difficult task since exercise alone without any environmental contaminants will cause a decline in expiratory flow rate or an increase in respiratory resistance in asthmatics. In the case of oxides of nitrogen, we have recently been given the results of an acute exposure experiment in asthmatics,[1] which indicates that this gas in relatively low concentration enhances the response of the asthmatic to a subsequent challenge by mecholyl. This is a good example of the value of such acute experiments. It has been suggested that an exacerbation of spontaneously occurring asthma is one of the earlier effects of oxidant pollution. The acute experiments on ozone have undoubtedly helped us to define better the levels at which significant airway obstruction develops, and have, in addition, given us an important idea of individual variation. We have also found evidence, I think for the first time, that the response to this gas, when acutely encountered, may be lower in those who customarily live in an area of relatively high oxidant pollution.

Taken together, these and many other studies give us a good idea of the kind of information that such acute experiments can provide. I would tabulate these advantages as follows:

- The determination of the earliest measurable physiological or biochemical effect.
- The study of individual variation and the modification of effects by other pollutants or by other factors such as exercise or heat.

- The study of individual adaptation or modification of a response by previous exposure.

- The study of the mechanism of action of the gas concerned and the relationship between early symptoms and changes in function.

Acute human studies are also important because they form a part of the total evidence of the effect of a pollutant, fitting between animal data and chronic exposure studies. It is when data from all three sectors begin to show some general concordance that we begin to be confident of the emerging picture. I do not believe that that picture can be satisfactorily completed unless acute human exposure data are made available.

As I have mentioned earlier, the surprise to me is that such acute studies have taken such a long time to be developed. I haven't much doubt that we still have a great deal to learn from such studies and I think that it is very important that the present tendency to discount or to make difficult such human studies should not discourage investigators from trying to undertake them.

OCCUPATIONAL EXPOSURE

In listening to a discussion on the precautions that must be taken by investigators to ensure that volunteers fully understand the nature of the risks involved in such experiments, it occurred to me to wonder whether, or how often, we apply the same standards in relation to occupational exposure. Are the hazards of asbestos discussed with those who are going to handle the material? Are workers in the rubber tire industry told about the increased incidence of bladder cancer in workers in some sections of that industry? Interestingly enough, a recent Royal Commission in Ontario[2] has recommended that because the radiation hazard of uranium was not explained to the miners in advance, and they were not told of the hazard of this exposure when paired with cigarette smoking, all men in that occupation who develop lung cancer should be considered eligible for full compensation.

I have a feeling that some people are unenthusiastic about acute human studies because of a particular perspective on the problems of decision-making. Their argument would run somewhat like this: "I am not interested in the level of a gas sufficient to cause reversible bronchospasm in a normal individual, unless you are prepared to tell me that reversible bronchospasm is a disease." I think this argument requires discussion. I note that the World Health Organization report on atmospheric pollutants laid down four categories of pollutant levels, which were designed to be helpful to those considering exposure guidelines. Their Level III reads as follows:

> "Concentrations and exposure times at and above which there is likely to be impairment of vital physiological functions or changes that may lead to chronic disease or shortening of life."

This is a convenient definition since obviously a concentration of the gas sufficient to cause acute airway obstruction is causing impairment of a vital physiological function. We therefore do not have to distinguish between that effect and the possibility of causation of a chronic disease in setting a pollutant level within the category of Level III.

I think that this objection to acute studies is really quite illusory. We are very likely to make a decision that concentrations of gases high enough to cause easily measurable impairment of airflow in normal people is not an environment that we should accept as strictly necessary or desirable. Those who would argue that reversible bronchospasm is not a "disease" are presumably prepared to argue that reversible bronchospasm can be safely ignored in the setting of ambient standards. As far as I am concerned, in that discussion the burden of proof rests with them to demonstrate that repetitive bronchospasm of that kind is not producing adverse effects, before we should accept that the environment that produces it should be considered acceptable for the general public. I do not feel therefore that this objection to acute studies, which is essentially an attitude of "we won't know what to do with the results when we get them," is one that should play much part in determining their appropriateness.

The other objections to acute studies have to do with the necessary artificiality of the protocol. This is unavoidable if you want to eliminate a good many variables present in the normal outdoor environment. But it may be a valid objection that ethical considerations prevent especially sensitive people from being studied and preclude studies on those whose cardio-pulmonary status is already compromised. I have already mentioned a recent acute study using nitrogen dioxide at very low concentration in which known asthmatics participated, so this objection is not absolute. However, we must recognize the fact that acute exposure studies are very difficult to do on some of the population groups we may want to protect. The answer here would be to get as clear a definition of effect in relatively healthy normal people in the first instance, and then be prepared to protect others by insisting on some built-in safety factor when determining safe levels for a population.

CHRONIC EXPOSURES

In my opinion, chronic experiments on pollutants are not really possible in the laboratory. I do not have a precise definition of chronic, but exposures lasting weeks or months do not seem feasible in terms of human experimentation, and therefore, the only "laboratory" that can be used for such studies is one in which individuals are already exposed to higher levels of some materials than are the rest of us. These chronic exposures give us an opportunity to study comparative morbidity in different occupational settings, and without doubt they are helpful in defining the upper level of exposure permissibility.

In the case of oxides of nitrogen, the studies of tunnel workers in New York exposed to relatively high concentrations of automobile exhaust indicated a probable upper level beyond which overt and obvious respiratory consequences would be detectable. In the case of sulphur dioxide, a recent study of smelter workers exposed chronically and intermittently to less than five parts per million of SO_2 will prove very valuable in indicating the consequences of exposure to sulphur dioxide at that concentration on ventilatory function. In the case of ozone, it would be helpful to have detailed knowledge of any deterioration or lack of it in welders or in air crew who are intermittently exposed to ozone levels high enough to cause characteristic symptomatology. The recent reports of acute ozone symptoms occurring in some flights from the United States to Alaska indicate the kind of opportunity that could be taken advantage of once the actual levels of ozone exposure were accurately known.

In the case of carbon monoxide, there are population groups exposed to high concentrations who may well be used to provide information on its long-term effects. Because of the common dissociation between those involved in environmental work and those involved in occupational medicine, there is a need for bridging the gap between the two disciplines, and there is certainly good use to be made of data secured in one kind of experiment in relation to decisions made in another sector.

There are valid objections to this kind of chronic study that are relevant to decision-making, particularly when they apply in the occupational setting. The work force that is exposed to these materials is not the same as the general public. It is sometimes argued that, with a specially selected work force and careful medical surveillance, higher exposure levels may be tolerated than you would allow for the population at large. But such a point of view often takes for granted the existence of detailed and precise medical surveillance, which, in my experience, is not often a reality. In spite of these objections, every opportunity must be taken to make measurements of individuals breathing higher concentrations of some materials than the rest of us, and I cannot see anything wrong with that kind of scientific opportunism.

The whole field of epidemiological study may be viewed as the logical way for us to begin to understand effects. In respect to carcinogenesis, of course, it is the only tool open to us except for laboratory testing of suspicious materials.

STANDARD-SETTING

Before I conclude, I wish to reflect on the relationship between all these modes of experimentation and decision-making on standards. It seems to me that it is the concordance of data that provides the most convincing case on which defense of any single number for human exposure can be successfully mounted. There are, however, some other considerations that I feel I should draw to your attention.

First, in reading the voluminous and expanding literature on standard-setting, I think it is as well to remind ourselves that the essence of the standard-setting process is to be able to advance a hypothesis on the basis of the best information available. The hypothesis may be simply that exposure of a normal population to not more than some level of a contaminant will not have any adverse effects on the physiological function of the individual, nor any long-term effects on his health. I would argue that this kind of hypothesis is not greatly different from the kind of hypothesis that scientists are constantly advancing in respect to laboratory experiments, and the deductions that may be drawn from them. There is sometimes a tendency to blur this essential similarity by arguing that in one case the scientist is dealing with "hard fact," and in other cases, the information is relatively soft.

We can also recognize that it is quite easy to frame questions from the political sector that are beyond the scope of any kind of scientific experiment to answer in any precise way. However, what is being attempted in the standard-setting process is to look carefully at some hundreds of scientific papers and to distill from the accumulated data the best available hypothesis for protection of the public.

In that endeavor, both acute and chronic studies are necessary, and there doesn't seem to me to be any reason to favor one kind of study over the other, since they answer different kinds of questions and provide a different sort of information. What seems to me to be indisputable is that both kinds of information are needed, as is the information we get from animal toxicological studies, and one in no sense excludes the value of the other. The initial title I was given to address on this program perhaps suggested that there was some kind of competition between the two kinds of studies I have talked about, but this doesn't seem to me to be an appropriate attitude. What seems to me more necessary to emphasize is how little of this general work has been done in view of the obviously pressing nature of the questions that naturally arise from the man-made environmental deterioration to which most of us are exposed.

Second, I feel that in the acute studies and, indeed, in some of the chronic ones, there is a special advantage in studying physicians. Our initial studies of 0.75 parts per million of ozone[5] were all done on physicians for several reasons. They could be presumed to understand fully the nature of the risk; they might be specially capable of recording early symptoms; and we felt we could rely on them to discontinue the exposure if untoward symptoms occurred. In some situations, therefore, there is a special merit in adopting that kind of protocol. In chronic studies too there are some advantages to studying physicians and you will remember that Dr. Richard Doll's original study on cigarette smoking and lung cancer was based on a prospective study of British doctors, partly because he expected that the diagnosis would be more accurate in them, and also because he hoped that he would have a lower dropout rate.

Third, I think we should not only view our work as being necessitated by questions that society is insisting should be answered, we should accept the responsibility of generating the questions and of working towards knowledge that we can see is going to be needed, often in advance of any public appreciation that the questions are indeed important. It is important to preserve the opportunity for innovative research in advance of public opinion.

In that connection I might end by telling the story of the encounter in the street at night between a slightly inebriated man who was circling around under a street lamp, and a helpful passerby who asked him what he was doing. "I have dropped my keys somewhere," the first man said, and the second joined him in looking for them. After a few seconds, the second man inquired, "Are you sure you dropped them here?" And the first man replied, "No, but this is where the light is." In reviewing our research effort, we must always make room for the important idea in a field not yet illuminated by the glare of public attention.

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Discussion Summary

Participants discussed the problem of distinguishing defense mechanisms from toxic responses in the lower dose acute studies. Whether or not they trigger reversible or irreversible changes, defense mechanisms cannot be equated with toxic responses. Some participants questioned the exact meaning of "toxic response." For example, sweating is a normal non-toxic response to heat, but excessive heat, even with the sweating response, can kill a person.

Further discussion focused on the phenomenon of a repetitive stimulus that provokes a physiological response. Participants noted that evidence is mounting to indicate that a repetitive stimulus that causes a physiological response may produce long-term adverse effects. For example, a follow-up study of 18-month-old infants afflicted with bronchiolitis revealed that at ages seven to ten, these children showed compromised pulmonary function. Participants agreed on the need for more follow-up data and acute studies on repetitive stimuli.

Participants also discussed the trend away from controlled experimental studies that last longer than twelve hours. Studies of this duration were not thought to be useful to the researcher for two reasons. First, most exposures occurring in the environment are episodic; for example, an exposure to a pollutant. Thus, a study that exposes a subject to a pollutant for an extended time period would not be a valid model for an investigator.

Second, studies that run longer than twelve hours are not long enough to be valid models for studying long-term effects. For example, if a researcher were interested in studying the effects of long-term exposure to sulfur dioxide, the appropriate study subject would be a smelter worker who had been exposed to the substance for the last five years. Thus, the experiment that lasts longer than twelve hours is usually too short or too long to be practicable.

Role of Automatic Data Processing in Clinical Research

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When discussing automatic data processing in the setting of clinical research, it is helpful to have a sharp idea of what clinical research is. For this discussion, we will define clinical research as the activities associated with acquiring and transforming clinical or patient experiences into knowledge. This knowledge allows us then to predict or anticipate outcomes, given a characterization of a patient and his surrounding environment. This knowledge of patient-environment interaction is thus helpful not only in establishing effective treatment, but also in developing policies for maintaining our surroundings that are compatible with a desired quality of life.

The basic tool of the clinical investigator is the stimulus-response experiment. Experimental preparations are characterized, as well as the stimulus or change in environment with which the preparation exists. Certain signals representing function of the preparation are monitored over time and changes are detected. Because signals sometimes contain variations over space or time that seem unrelated to the experiment, a control study is usually carried out where the environment is standardized. Thus, changes in the monitored signals obtained from the experimental study are considered significant only when they exceed the changes observed in the control study.

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SOFTWARE

Data processing plays a number of roles in the support of clinical research as described above. First, signals from patients or experimental subjects must be acquired. These signals usually contain much redundancy and therefore are not dealt with in their virgin form. The signals are first transformed into a set or sequence of primitive elements.[1,2,3] These primitives are assumed to allow adequate description of the original signal. The representation of a signal by a sequence of primitives is called a message. As an example, when dealing with the electrocardiogram we can choose several classes of primitives to construct a message. One class contains the characters p, q, r, s, t, _ where each character represents a certain feature. A message constructed from this set of primitives might appear as

p _ q r s _ t _ _ _ p _ q _ r s _ _ t _ _ _

Another class of primitives might be the set of integers where the integer selected is the amplitude of the signal at a point in time. Thus, the sequence

1 2 3 2 1 0 0 -1 -2 -3 -3 -2 2 4 10 20 10 4 2

-2 -3 -2 -1 0 0 0 0 1 2 3 2 1 0 0 0

is a message representing the same EKG signal, but constructed from a different set of primitives.

Many times these primitives can be detected automatically by a signal-processing computer. Such automatic signal processing is helpful. It reduces the time between signal acquisition and signal analysis, as well as providing a high degree of consistency in the pattern recognition.

Messages comprised of sequences of primitives describe the various facets of a clinical experiment. However, to be useful, features must be derived from messages and organized in a manner that is appropriate for data analysis.

Data management is a second role where computing can provide considerable aid. The data management component of supporting clinical research consists of both deriving features from incoming messages and distributing messages, message components, and derived features to various user data files. The bulk of data management activities can be classified as file management and as such, can be considered disjoint from both the data acquisition and data analysis activities.

Although feature recognition is not usually considered part of data management activities, I would submit that it, in fact, is. Feature extraction or recognition, such as computing heart rate from the EKG, many times does not need to occur in real time as does data acquisition. Therefore, it can and probably should be deferred to minimize the overhead during data acquisition. The logical place to put feature selection is in the activity that deals with message and file management, i.e., the data management activity.

Another reason for considering feature extraction as part of data management is that it tends to be evolutionary in nature. For instance, during the early phase of an experiment, heart rate may be the only parameter thought to be of interest. However, as the experiments progress, it is observed that S-T segments really seem to reflect the stimulus and therefore should be analyzed. If the original data were represented in sufficient detail by primitives, then this new feature could be extracted from old studies without reacquiring the primary data. This activity is clearly data management.

Data analysis is perhaps the most difficult area in the support of clinical research. Because data analysis tends to be evolutionary during the life cycle of a research project, the tools for supporting analysis must be flexible. It is here that the flexibility of a computer can be used to a considerable extent.

Data analysis is the combination of selecting subsets of the original database, and analyzing selected variables within these subsets or comparing subsets. Since the degree of subsetting cannot be easily forecast, it is important to organize a data file in such a way that subsetting is easy. For this reason, a flat file or matrix file is a useful data structure.[4] The rows of the matrix represent instances of the research protocol (1 row = 1 patient), while the columns represent the data values of various parameters. The matrix can be represented in either row order (direct file) or column order (transpose file). The transpose representation is most useful for subsetting, while the direct file is most useful for data analysis.

In a computing system supporting data analysis, flexibility is achieved by avoiding the binding of variables in a user program directly to columns in the matrix. By interposing a dictionary that associates variable names with column positions between the user program and the data files in the matrix, the accessing program can avoid the need to know the exact location of variables in the file structure. Thus, adding or changing variables simplifies modifying dictionary entries, while the software driving the data analysis remains unchanged. Program maintenance is minimized using such dictionary driven databases.

HARDWARE

The partitioning of research support activities into data acquisition, data management, and data analysis leads naturally to a distributed view of the hardware used to implement these activities. In our own laboratory, we have developed the support software in such a way that the communication between data acquisition, data management, and data analysis is relatively clean and well-defined. A clean interface then makes it possible to support various components on a variety of hardware devices. For instance, while text based data entry (history, physical, etc.) is supported by the computer that primarily manages the database, some of the graphic data entry activity is supported by remotely located microprocessor based systems. In addition, while some data analysis is performed by the data management machinery, we also utilize the resources of our university computation center.

The point of all this flexibility is to allow for the known unknown, that is, we all know that tomorrow we would like to improve some aspect of the experiment but we don't know exactly what. Decentralizing data acquisition in particular is very helpful in this regard. If a small micro or mini computer supports some phase of data acquisition, it can be changed without much involvement of other hardware/software functions, whereas centralizing this activity does not lead to easy change. Similarly, if the data management strategy is supported on a dedicated system, it too can be modified without much long-range effect. With machine costs dropping, such an approach appears viable. Task switching overhead is minimized at the cost of increased communication cost between systems. It will certainly be interesting to watch the progress over the next few years.

SUMMARY

Automatic data processing can be used as a profitable adjunct in clinical research. When properly developed, ADP can increase the flexibility of data acquisition, data management, and data analysis over manual systems. It allows the investigator freedom of choice in the evolution of his experiment by holding open data interpretation and analysis options as long as possible. The complexity of today's experiments is great, and the manual tools in many cases are not adequate to deal with that complexity.

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Discussion Summary

In a discussion of the computer operator's role in processing clinical data, participants said that the increased reliability on the operator to review complex records as they are processed increases the reliability of data analyses. This is true particularly in those instances where the computer program does not seem to be acting reliably or where extraneous signals are coming in. Participants said that in some cases, the computer operator is a laboratory clinician.

Some of the discussants prefer to use an automatic data acquisition system that eliminates the necessity for operator interaction. Participants said this procedure ensures that an objective data base will be produced. These discussants felt that using operators in the data review process introduces an element of doubt as to the reliability of the resulting data base.

Participants also discussed the role of automatic data processing in patient care. When the patient enters the hospital, an intern records his medical history and chief complaints on a check list form distributed by the data processing laboratory. Next, the laboratory determines whether the patient's data is accurate by checking the collected data against other hospital test results. If there is a discrepancy between the laboratory data and hospital test results, the patient is re-examined.

Discussants said that automatic data processing improves the quality of patient data by double checking its accuracy.

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ENVIRONMENTAL AND PHYSICAL SAFETY CONSIDERATIONS IN HUMAN EXPOSURE FACILITIES

Moderator: Russell Pimmel, Ph.D.

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Environmental Controls and Safeguards

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The test environment, and, in particular, the exposure atmosphere, are of primary concern in controlled inhalation studies. There are many physical factors in the test environment that can affect the results of an experiment. Temperature, humidity, light and noise levels, and many other factors need to be stabilized, controlled, and described adequately. However, considering the focus of this conference, it seems most appropriate to emphasize the exposure atmosphere.

It is necessary to control the environmental variables in an exposure atmosphere for two basic reasons. One reason is to protect the subjects from accidental exposures and overexposures. The other reason for controlling environmental variables is to protect the integrity of the experiment. If, because of faulty instrumentation or sloppy work, the subject is exposed to the wrong level of contaminant, the integrity of the experiment becomes questionable. Extraneous materials in the exposure atmosphere can also affect an experiment's results.

The integrity of the exposure level must be assured in order to interpret the experimental data accurately. For example, slug exposures may elicit different responses than steady exposures, and although we generally design experiments to have a constant level of exposure, we do not always achieve it. In some of the older studies, which were performed without the aid of modern instrumentation,

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investigators had variable exposure levels during the course of an exposure. Sometimes the reports simply indicated the average concentration, without any indication of how much the exposure level varied.

DESIGNING A FAIL-SAFE EXPOSURE SYSTEM

There are some basic principles of control which are used in designing a fail-safe exposure system. Control valves can be either normally open or normally closed, and must be energized to turn them to their alternate position. Such controllers will revert to their normally open or closed mode when the power fails. Clearly, in designing a test system involving human exposures, the investigator would want to make sure that whenever there is a possibility of equipment failure, the exposure would be reduced or stopped, or at least maintained at a near constant level. The investigator cannot have a system where the supply valve of a gas bottle is left open at the same time that the ventilation or dilution air closes down because of a fan failure. This could lead to the subjects being over-exposed to the test substance, with possible serious consequences. In addition, the integrity of a whole series of experiments could be ruined.

Another principle or variable that has to be considered in experimental design is the temporal response of the test system. How rapidly can the exposure concentration be raised or lowered to achieve the appropriate level of exposure? If the concentration starts to go up or down for reasons extraneous to the experiment, how rapidly can the investigator bring it back? How quickly can he take action, either manually or automatically, that will keep the concentration within prescribed tolerance limits? These are the basic elements of feedback response that have to be considered in the experimental design, and these variables are part of the specifications investigators have to establish in the fabrication or construction and installation of test equipment.

A selection must be made between manual and automatic control of the test environment. How much automatic control is necessary or desirable, and how much interaction should there be between the analog output of concentrations and the individual operator or mechanical controller who is doing the fine-tuning of the concentration? Clearly, for most investigators, the answer to this question depends not only on what method is ideal, but also on what method is compatible with the budget. The absence of sophisticated automatic controls and data processors need not limit experimentation. With adequate means of manual control, many kinds of experiments can be performed quite successfully.

Redundancy is important in the generation, monitoring, and control of the test atmosphere. We do not want an experiment interrupted or endangered by the failure of one component of a system. It is relatively inexpensive to provide alternate means of at least monitoring and controlling the concentration. This way, if one element fails, the investigator can finish the day's experiment on the back-up system and not have to worry about losing control of the experiment or terminating it prematurely.

Finally, the investigator must be somewhat compulsive about all the problems that could occur in the experiment, and have contingency plans to follow in the case of an emergency, in order to protect the subjects and the integrity of the experiment.

FORMATION OF THE EXPOSURE ATMOSPHERE

The first consideration in a discussion of test atmospheres is methods of atmosphere generation. This discussion will be restricted to areas relevant to human studies, primarily concentrating on the ambient pollutant gases and aerosols of both oxidizing and reducing atmospheres. Current studies involve chambers and exposure equipment for studies with sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), carbon monoxide (CO), and sulfur oxide (SO_x) particulates.

GENERATION OF GASEOUS ATMOSPHERES

Carbon monoxide, sulfur dioxide, and nitrogen dioxide are readily available as bottled gases, and we do not have to worry about extraneous contaminants being introduced in the process of generating the gas. On the other hand, for gases formed in chemical conversions, other products might be introduced during the reaction process. There are well-established systems for metering compressed gases into a dilution airstream to serve as the exposure atmosphere. Both SO_2 and NO_2 are highly corrosive vapors, and should only be passed through chemically resistant lines. For NO_2, which condenses to a liquid at room temperatures, the lines must be heated.

Ozone, which is a very reactive and unstable gas, cannot be bottled. The conventional system for generating ozone uses an ultra-violet light source to form ozone from atmospheric oxygen.

Aerosols, of course, cover a broad range of chemical composition. An aerosol is a suspension of particles in air. These particles can be either liquid or solid, and they come in all different particle sizes. One specific aerosol used in several current human studies is sulfuric acid. Other human studies have used other SO_x aerosols; in particular, ammonium sulfate and ammonium bisulfate.

AEROSOL GENERATION

All of the SO aerosols are soluble in water. The general technique for generating such aerosols into human exposure environments is to use a nebulizer, which shears a liquid into a stream of fine droplets of the appropriate size. The size of the droplets is somewhat controllable, depending on the design of the nebulizer, and whether it is driven by compressed air or an ultrasonic transducer. The particle size is also affected by the concentration of the chemical in the water being nebulized.

The nebulizer can generate a limited range of droplet sizes, and since the equilibrium size depends on the humidity of the air, the generators produce both water vapor and droplets, which are more concentrated in terms of the solute than the liquid being nebulized.

Using conventional nebulizers, the investigator can readily generate particles whose predominant size ranges from 0.1 to 1 micron. This is usually an appropriate size in air pollution studies, because a large part of the SO_x aerosol in the atmosphere falls into this size range.

A single particle size is not generated by any conventional nebulizer. The investigator generates a particle size dispersion, a so-called hetero-dispersed or poly-dispersed aerosol. This is not necessarily a bad technique, in that it produces an integral exposure that corresponds to the exposure people are exposed to in the environment. On the other hand, in calibrating our systems for their response and the response of our monitors for particles, response is usually very much dependent on particle size.

MONO-DISPERSED AEROSOLS

Sometimes mono-dispersed (particles of the same size) laboratory aerosols are needed. There is no uniform method of generating a mono-dispersed calibration or test aerosol over the entire range of particle sizes. The particle sizes that we are concerned with run from about a few hundredths of a micron to ten microns.

The vibrating orifice generator (Figure 1) is one method of mono-dispersed aerosol generation in general use recently for particles of about one micron and larger. A pressurized liquid stream is forced through a small hole, which is either three, five, or ten microns in diamteter, depending on the desired size range of the droplets. An aerosol will form when the liquid stream is forced through the hole under pressure. However, such aerosols will be relatively large and hetero-dispersed. If this technique is combined with a high frequency electrical disturbance, which translates into

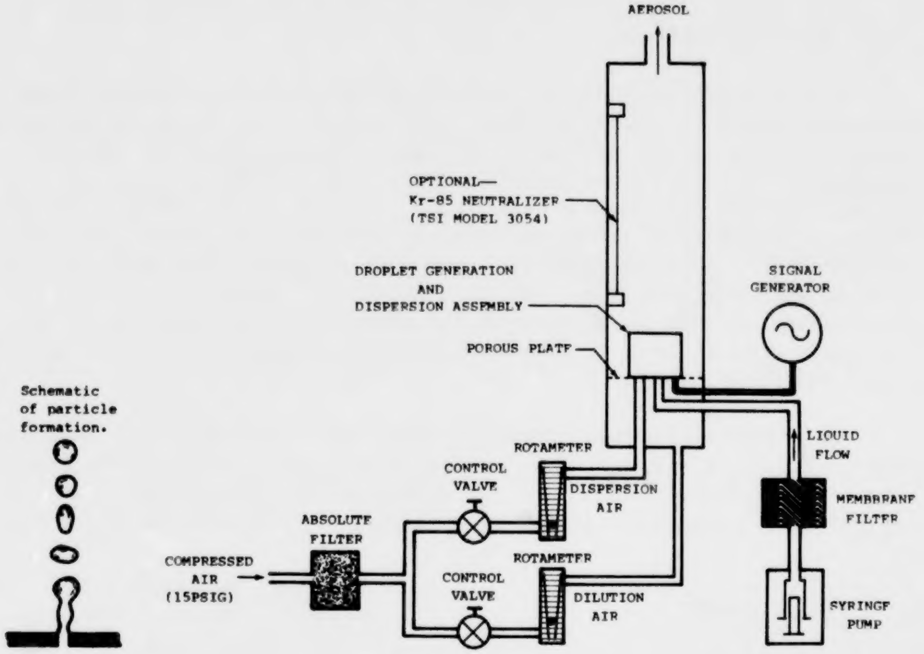
AEROSOL
OPTIONAL—
Kr-85 NEUTRALIZER
(TSI MODEL 3054)
DROPLET GENERATION
AND
DISPERSION ASSEMBLY
SIGNAL
GENERATOR
POROUS PLATE
Schematic
of particle
formation.
LIQUID
FLOW
ROTAMETER
CONTROL
VALVE
DISPERSION
AIR
MEMBRANE
FILTER
ABSOLUTE
FILTER
COMPRESSED
AIR
(15PSIG)
ROTAMETER
CONTROL
VALVE
DILUTION
AIR
SYRINGE
PUMP

Figure 1. Schematic diagram of vibrating orifice aerosol generator. Source: TSI, Inc., literature.

a mechanical disturbance, the investigator can make the jet break up into uniform droplets. With an appropriate frequency applied to the piezo-electric transducer, the droplet size will be about three.

With the vibrating orifice, the investigator can produce droplets with a geometric standard deviation as low as 1.02, or just as mono-dispersed as possible in a laboratory, and comparable to the dispersion nature achieves with various pollens. Residual solid particles of a much smaller size can be obtained by using dilute liquids. This method is preferred for forming particles larger than one micron.

A system cannot be run reliably with an orifice smaller than about two or three microns in diameter. So, the investigator is limited to droplets of six to eight microns and to solid particles of about half a micron at the smallest.

For the larger size particles, there is an alternate to the vibrating orifice technique, the spinning disc, which produces aerosols of essentially the same size range and concentration as the vibrating orifice.

A different technique can be used to produce a narrow range of particle sizes in the very small size range. As shown in Figure 2, mobility classifier introduces the aerosol with unit electrical charges at an outer annulus of a cylinder, and the particles migrate toward the central electrode, propelled by their electrical charge. There is a clean air sheath that all the particles have to traverse. This is important because it means that all particles have essentially the same radial distance to cross the central electrode. If the particles of the same mobility came in across the whole cross section, those that started nearer to the electrode would reach it first.

In a poly-dispersed aerosol, where all the particles have one charge, their migration against the aerodynamic drag of the airstream toward the central electrode is determined by their size. If, at this point, there is a place to withdraw the aerosol on the electrode,

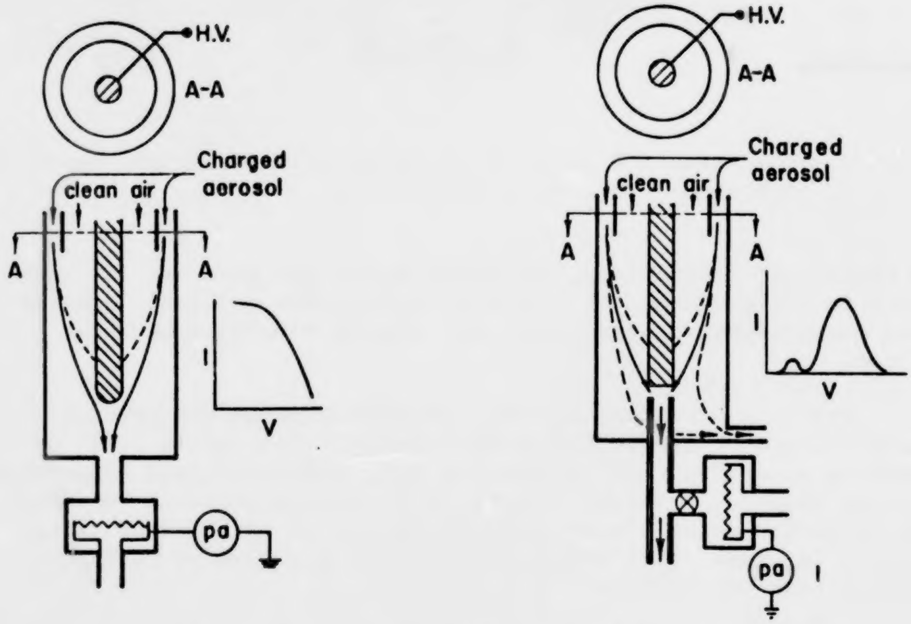

Figure 2. Schematic diagrams of electric mobility analyzer tube as used in mobility size analyzer (left) and as particle separator (right). Source: Fine Particles (Liu, B.Y.H., ed.). Academic Press, 1976, p. 599.

only particles of a very limited range of electrical mobility and particle size will be directed there. The aerosol drawn through the open path will have a narrow range of particle sizes. One can vary the particle size range drawn out at that point by varying the air flow velocity or the voltage differential. This, in effect, enables the investigator to go from a few hundredths of a micron up to about half a micron in mono-dispersed aerosol generation.

This technique is inefficient in that only a fraction of the generated poly-dispersed aerosol is used. However, if the investigator is using a dye or some relatively inexpensive material as a calibration aerosol, this disadvantage presents no great problem.

This technique cannot be used for larger particles because at above about half a micron, the particles tend to have more than one charge and can no longer be sorted according to their mobility.

MONITORING THE EXPOSURE ENVIRONMENT

There are various approaches to monitoring the exposure atmosphere and characterizing the concentrations of the chemicals to which subjects are exposed. The traditional and simplest monitoring technique is manual sampling, where the investigator draws a known volume of air at a known flow rate through a collector. For particles, the collector can be a filter; for soluble gases, it can be a bubbler; for organics, it can be a charcoal trap. The appropriate collector is used to trap particles with known, and presumably, high efficiency.

For gases and vapors, the collection efficiency needs to be known and constant. If it is less than 100 percent, the amount collected can be corrected to compensate for the lack of total collection. For aerosols, on the other hand, there must be 100 percent collection efficiency, since the collection efficiency is particle size-dependent, and the investigator wants to know the total amount, and not some estimate that varies with its particle size distribution. In practice, this requirement doesn't cause any great problem, since filters and other types of collectors with essentially quantitative collection capabilities are readily available.

One advantage of sample collection and subsequent analysis is that there is almost no limit in the choice of sample processing that can be done, or in the range of sophisticated and sensitive laboratory instruments that can be brought to bear on analytical problems. The investigator can get the ultimate in sensitivity and specificity, with correction for interferences. On the other hand, there is a basic limitation in this procedure in that there is a significant time lag between sample collection and the determination of what was collected. Manual sampling techniques may, therefore, be used to back up continuous monitors, and perhaps, as the final arbiter on a substance's exact concentration. However, in themselves, they are not of much use in maintaining an atmosphere at a desired level.

INTERMITTENT/CONTINUOUS INSTRUMENTATION

Generally, therefore, investigators use two basic types of automated instrumentation. One is the intermittent type of operation, and the other is continuous. For monitoring particles, a combination of techniques is generally used because there is a very large particle range to be covered, and there is no universal instrument that can indicate the concentration of each particle size interval over the entire size range.

One of the instruments used to measure very small particles (0.08 μm to 0.5 μm) is a close relative of the mono-dispersed small particle generator. As shown in Figure 2, the electrical aerosol analyzer works on the same principle of sorting out the particles of a poly-dispersed aerosol according to their electrical mobility. Instead of withdrawing the particles at a specific location on the axial electrode, they are collected on a current collecting filter at the end of the tube, and the amount of charge they deposit on that filter is measured incrementally. The voltage gradient and/or the flow rate is changed sequentially to allow a different size cut to reach the filter. In this way, there is a progression of size increments. This technique gives the investigator an accurate size distribution in a stable atmosphere, and, of course, attempts are made to keep the chamber atmospheres stable. On the other hand, it takes a finite amount of time to run through these increments and collect the size band data to get the size analysis. This technique is an example of an intermittent operation.

In many cases, this technique is unsatisfactory, especially if the investigator wants very tight control of the substance's concentration, and needs a technique that senses the particles in a dynamic system and continuously indicates precisely what the level is. Investigators working with carbon monoxide can use an infrared analytical technique, which does not collect the sample at all. As shown in Figure 3, it simply directs the gas through the sample tube, through which also passes infrared radiation at wavelengths that are sensitively absorbed by carbon monoxide. There will be an attenuation of that infrared wavelength because of the absorption of the carbon monoxide in the sample tube, and, thus, the energy received on the detector will vary with the substance concentration. Operationally, this technique is best implemented by using a reference tube of clean air, and getting the difference in attenuation between clean air and the air containing the carbon monoxide.

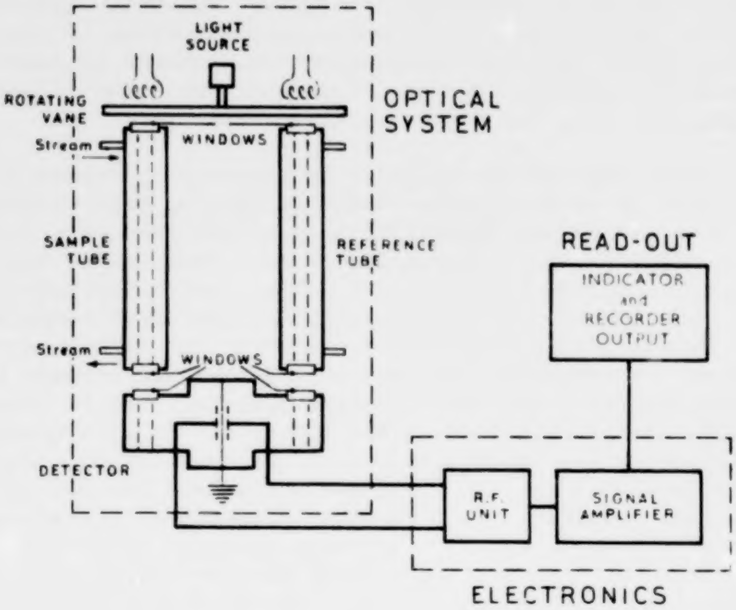
LIGHT SOURCE
ROTATING VANE
OPTICAL SYSTEM
Stream
WINDOWS
SAMPLE TUBE
REFERENCE TUBE
READ-OUT
INDICATOR and RECORDER OUTPUT
Stream
WINDOWS
DETECTOR
R.F. UNIT
SIGNAL AMPLIFIER
ELECTRONICS

Figure 3. Schematic diagram of infra-red gas analyzer. Source: Air Sampling Instruments (5th edition). ACGIH, Cincinati, Ohio, 1978.

Other gaseous constituents absorb infrared energy; for example, water vapor. However, these gases and vapors are wavelength-specific, so by tuning to the wavelength at which carbon monoxide has preferential absorptive capacity, the effect of interference can be removed, giving a sensitive, accurate, and specific analysis of carbon monoxide. The only time lag is the insignificant amount of time it takes to flush the sample through the tube. This, then, is a commonly used method of monitoring carbon monoxide on a continuous basis. The sensitivity is a function of the length of the sample tube, which can be 10 or 20 meters with folded tubes.

There is practically no limit in the laboratory situation to the sensitivity that can be achieved using this type of instrumentation. Similar instruments can also be used in measuring other gases by choosing appropriate wavelengths of absorption free of significant interferences.

An alternate method of testing carbon monoxide is an intermittent technique, which involves a combination of gas chromatography and flame ionization detection. The flame ionization detector is nonspecific, but by coupling it with the holdup time in the chromatographic column, specific analyses can be obtained because the investigator knows when the carbon monoxide will come through the column and move into the flame ionization detector.

The flame photometric detector illustrated in Figure 4 is commonly used in measuring the concentrations of sulfur-containing gases. If a sulfur-bearing material is passed through a hydrogen burner, a light photon emission will result that can be detected with sensitive photomultipliers. It is a nonspecific technique in that it gives the investigator roughly an equivalent response for hydrogen sulfide, sulfur dioxide and some of the mercaptans. So, if the investigator knows that the only sulfur gas present is sulfur dioxide, then the test is quite specific, but if there are other sulfur gases, the test is not specific. In this instance, the investigator can attach the sulfur gas detector to a chromatographic column that will separate out the sulfur species so as to make the test specific. In laboratory situations, the procedure is usually unnecessary.

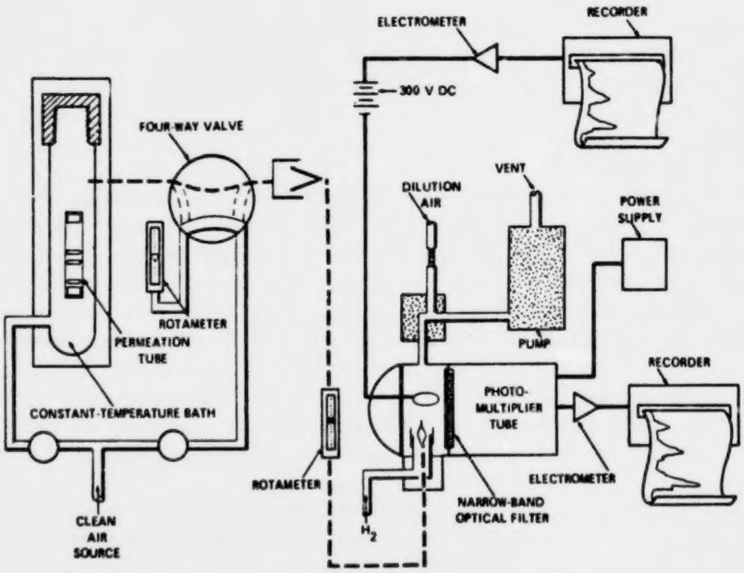
ELECTROMETER
RECORDER
300 V DC
FOUR-WAY VALVE
VENT
DILUTION AIR
POWER SUPPLY
ROTAMETER
PERMEATION TUBE
PUMP
RECORDER
CONSTANT-TEMPERATURE BATH
PHOTO-MULTIPLIER TUBE
ROTAMETER
ELECTROMETER
NARROW-BAND OPTICAL FILTER
CLEAN AIR SOURCE
H_2

Figure 4. Schematic diagram of flame photometric analyzer for sulfur gases, with permeation tube calibrator. Source: Air Sampling Instruments (5th edition).

In most situations, it is desirable to have a built-in calibration device on the concentration monitor to ensure that the concentration indicated on the output chart or on the dial is correct. One of the more common devices used for in-line, continuous calibration is the permeation tube. For the flame-photometric detector, the calibration device shown in Figure 4 contains liquid sulfur dioxide sealed into a Teflon tube. The tube is slightly porous to the saturated sulfur dioxide vapor above the liquid in the tube. The rate of permeation of sulfur dioxide vapor out of the tube is very much dependent on the temperature, but is constant at a given temperature. If the investigator holds the permeation tube within a constant temperature bath, he can obtain a known emission rate. If he gets an accurately calibrated dilution air flow, he can determine the concentration of the calibration gas and direct it periodically into the analyzer to get a span signal for the instrument. This is a very convenient way of calibrating. There are similar calibration tubes available for nitrogen dioxide, and a number of hydrocarbons that are readily condensed into liquids at approximately room temperature.

Instruments that measure the light emitted during gas phase reactions of nitric oxide and ozone are used in monitoring concentrations in chamber and ambient atmospheres. If an excess of ozone is mixed with the sample containing nitric oxide, as in Figure 5, the amount of light is proportionate to the amount of nitric oxide.

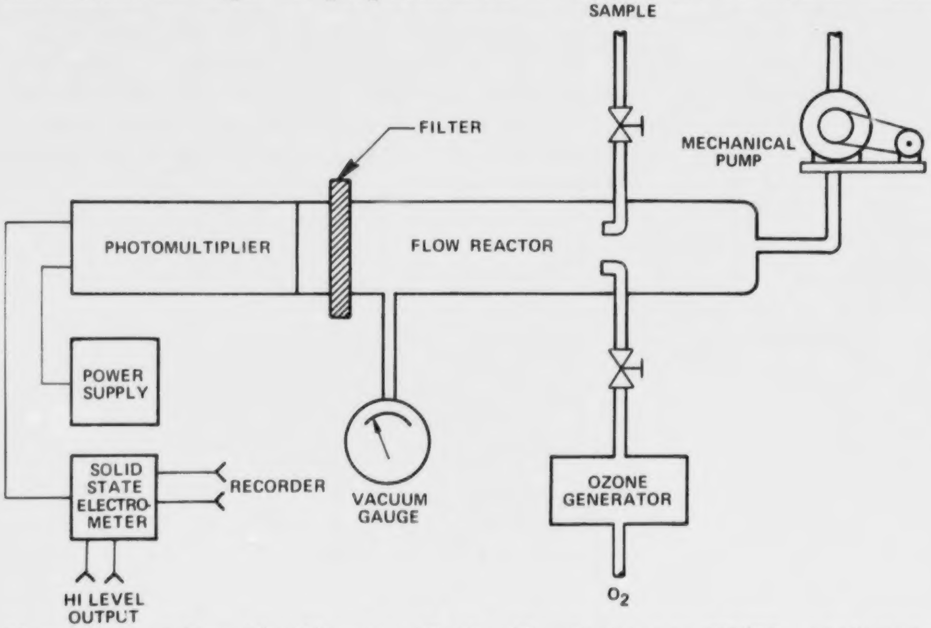

Figure 5. Schematic diagram of chemiluminescense NO/NO_x analyzer. Source: Scott Research Labs literature.

This technique can be used for measuring nitrogen dioxide by passing the sampled air through a chemical converter that converts the nitric dioxide to nitric oxide, which can then be measured on a mole for mole basis. The investigator can differentiate between nitric oxide and nitrogen dioxide by sequential readings with and without the converter in-line.

The same basic type of instrument can be used as an ozone monitor by feeding an excess of nitric oxide into the reaction chamber. Other ozone monitors are based on other chemiluminescent reactions of ozone, specifically, with ethylene and organic dyes.

I indicated before that the mobility analyzer could be used as a particle size analyzer for small particles, but that even using this technique, we could not measure particles larger than approximately a half micron in diameter. Fortunately, there are other techniques suitable for measuring the larger particles.

The property of light scatter is used in measuring the concentrations and size distributions of particles of three-tenths micron diameter and larger. When light is focused on a particle in the instrument illustrated in Figure 6, some of that light will be scattered. The amount of light that a given particle will scatter depends on its size. A photomultiplier can be used to detect the light output from each particle. The pulses can be accumulated according to size intervals in a multichannel pulse-height analyzer, and these intervals can be calibrated according to particle size. However, this technique is not as simple as it sounds. There are other properties of the particle besides its size that affect the amount of light scattered, including the refractive index, the color, the shape, and so forth, and reliable data depend on accurate calibrations of the instruments used.

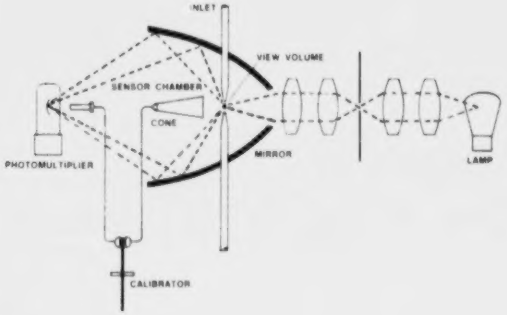

Figure 6. Schematic diagram of single particle optical particle size analyzer. Source: Climet, Inc., literature.

Investigators in the laboratory working with droplet aerosols or aerosols of fairly regular shape, have fewer problems than investigators working with particles in the ambient air, which come in a great variety of compositions and shapes. Thus, in the controlled laboratory experiment, a reliable calibration can generally be developed relating the optical-inferred diameter to the real diameter. These instruments are not continuous monitors because they accumulate and sort the pulses for a given interval, and then display a distribution. However, the response time can be fairly rapid.

MEASURING THE PARTICLE'S MASS CONCENTRATION

Both of the methods described for measuring particle concentrations and size distributions, i.e., the small particle mobility analyzer and the larger particle light-scatter analyzer, measure the diameters of particles and sort them by so many numbers of particles in each size interval. Number concentration is important in many studies, but in studying toxicology and its effects on people or animals, the investigator generally needs to know the aerosol's mass concentration. Since the mass of a particle varies with the cube of the diameter and with the density, the investigator needs to know more than number distribution. On the other hand, the automatic machines accumulate a very good statistical base. The investigator comes up with fairly good approximations by using transformations to volume distributions. If the particles' density is determined, the investigator can calculate a mass median diameter distribution or a concentration.

While such data transformations may be justifiable in some cases, the investigator is not really measuring the property that is being reported. It is, therefore, sometimes necessary to directly determine the aerodynamic size distribution, since this is the distribution of sizes that affects deposition in the respiratory tract. If a system of somewhat redundant measurements can be justified, it is best to use a variety of complementary aerosol measurements involving light scatter, mobility, and aerodynamic properties.

The beta attenuation technique combined with a two-stage collection system, as illustrated in Figure 7, sorts the particles by their aerodynamic size and measures the mass in each fraction. Using this technique, the air enters an impaction jet at the top, and particles above a cutoff size, depending on their aerodynamic properties, will be collected on the back-up filter. The investigator can continuously monitor the mass of accumulated particles collected at each stage using the beta attenuation technique. A carbon 14 source is used as a beta emitter. The amount of β-radiation

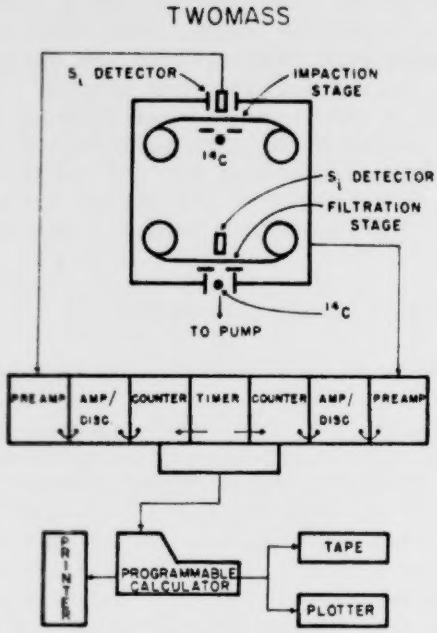
TWOMASS
Si DETECTOR
IMPACTION STAGE
14C
Si DETECTOR
FILTRATION STAGE
14C
TO PUMP
PREAMP
AMP/DISC
COUNTER
TIMER
COUNTER
AMP/DISC
PREAMP
PRINTER
PROGRAMMABLE CALCULATOR
TAPE
PLOTTER

Figure 7. Schematic diagram of TWOMASS mass concentration analyzer. Source: Fine Particles, p. 551.

that reaches the detector depends on the β-absorption in the accumulated sample between the source and the detector.

There is only about a 10 percent variation in beta attenuation with mass number (Z), with the exception of hydrogen, and hydrogen does not usually contribute much to aerosol mass. So, by and large, the amount of beta attenuation by the impacted particles on the first stage tells the investigator how much mass of material has been collected in large particles above the impactor cutoff size, and the attenuation of the particles on the second stage indicates the mass of small particles below the cutoff size. However, the response time of this technique is not very rapid, and may not be adequate for feedback control of generation rates in chamber atmospheres.

Another type of direct monitor of aerosol mass concentration utilizes quartz-crystal oscillators as mass balances, and is illustrated in Figure 8. Very small sample masses can be detected as they accumulate on the quartz crystal oscillator. The quartz crystal is cut into a particular mode, and electrodes are attached

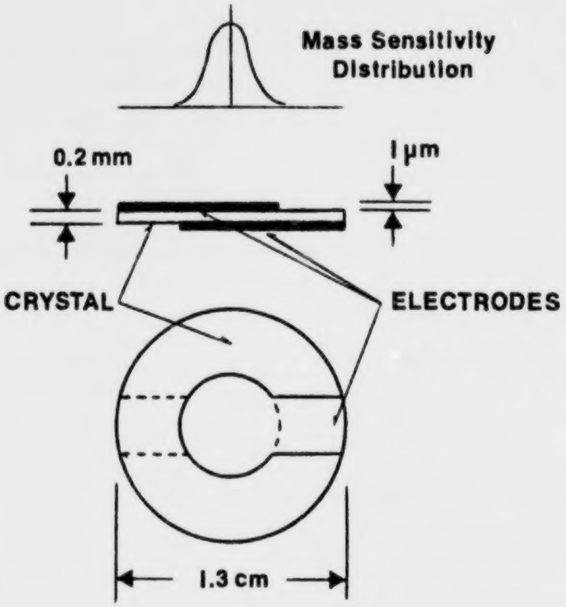

Figure 8. Schematic diagram of quartz-crystal oscillator used as a mass balance, showing sensitivity over crystal face. Source: Fine Particles, p. 489.

on each side. When a high frequency signal is applied, the crystal oscillates, and its oscillation frequency depends on the mass of the crystal.

When particles are deposited on the crystal, its mass increases and the oscillation frequency decreases, therefore, the sample accumulation can be measured by the change in the frequency of the oscillator. In modern instrumentation, frequency counting is relatively simple and precise, and very sensitive. Thus, infinitesimal masses produce readily measurable signals.

However, this technique has its limitations. The sensitive zone does not have a uniform sensitivity. It is greatest at the center of the electrodes and falls off toward the periphery. However, it does provide a sensitive indication of mass, and with enough calibration to be sure of its performance under the given operating conditions, can be used as a sensitive mass monitor.

Another instrument that can be used to provide an approximation of mass concentration of particles in the one-tenth to one micron range is the integrating nephelometer, which is illustrated in Figure 9. This technique measures the total scatter of an

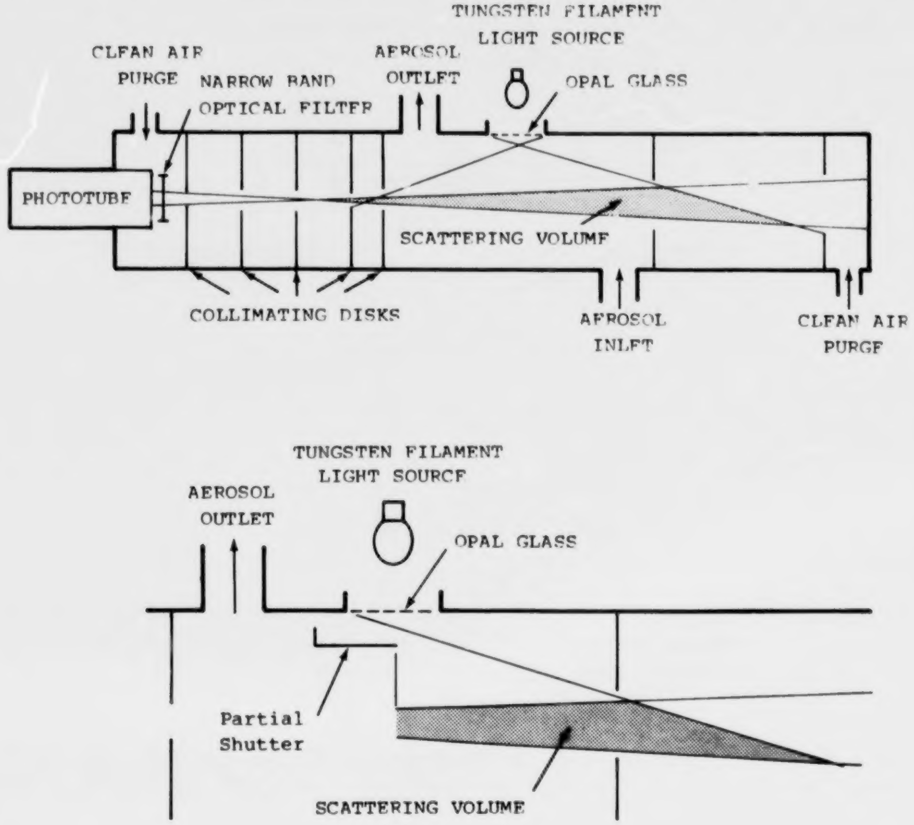
TUNGSTEN FILAMENT
LIGHT SOURCE
CLEAN AIR
PURGE
NARROW BAND
OPTICAL FILTER
AEROSOL
OUTLET
OPAL GLASS
PHOTOTUBE
SCATTERING VOLUME
COLLIMATING DISKS
AEROSOL
INLET
CLEAN AIR
PURGE
TUNGSTEN FILAMENT
LIGHT SOURCE
AEROSOL
OUTLET
OPAL GLASS
Partial
Shutter
SCATTERING VOLUME

Figure 9. Schematic diagram of integrating nephelometer. Source: Fine Particles, p. 521.

aerosol. The instrument discussed earlier measures the scatter from individual particles. The nephelometer, by contrast, measures the scatter of a cloud, i.e., the total scatter of all of the particles in the sensing zone.

If the investigator has the proper calibration and particles in the one-tenth to one micron range, he can obtain a correspondence between the total light scatter, the b-scat function, and the mass concentration. This gives the investigator a rapid response, and is a good indicator that nothing very drastic is happening to the atmosphere. This test may be a good monitor of the constancy of the atmosphere, even if it doesn't determine exactly what the concentration is.

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Discussion Summary

Participants asked Dr. Lippman two questions: 1) had he attempted to manipulate the orifice shape and jet stream pressure as a means of controlling particle size; and 2) had he considered combining the electrical charge aerosol generator with a fluidic vortex amplifier as a means of controlling power, speed, and size in the aerosol particles.

Dr. Lippman responded that he had no personal experience with either the vibrating orifice or the electrical charge analyzer. Participants agreed that the lack of uniformity of shape and diameter of fibers and other particulates present a real problem as far as monitoring and calibration are concerned.

Electrical Surveillance and Integrity

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Emergency Care Research Institute
Plymouth Meeting, Pennsylvania

INTRODUCTION

It is my pleasure to be able to discuss with you some of the many factors that contribute to the safe and effective use of electrically operated devices in human studies. In my discussion, I will draw largely on the experience of the Emergency Care Research Institute, which evaluates and tests devices and systems used for patient care. The Institute's testing spans both the field of diagnostic and therapeutic devices, a somewhat broader range than average. In general, I would judge that your interests would most clearly coincide with the diagnostic field in clinical medicine because as I perceive your work, you are recording physiologic variables primarily to assess the effect of stimuli acting on the subject.

While electrical safety in hospitals is related to two different aspects of the electrical shock phenomenon, commonly referred to as macroshock and microshock, it is my understanding that for the most part your concern would center on macroshock. Macroshock generally refers to electrical currents that occur through contact points on the surface of the body. Microshock occurs when currents penetrate the skin barrier through conductors and go to organs within the body. In general, microshock currents concern us less than macroshock currents.

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RISKS ATTENDANT TO THE USE OF ELECTRICAL DEVICES

This presentation will concentrate on electrical risks such as electrical shock, inadvertent or unwanted stimulation of excitable tissues, and electrocution. However, there are other risks that must not be overlooked, and any program that intends to ensure safe and effective use of instrumentation and systems must consider these risks. Additional risks in using electrical devices include the possibility of fire, especially in oxygen-enriched environments; burns; the subtle effects of chronic exposure to otherwise subthreshold electrical currents; or electrical and/or magnetic fields and mechanical trauma that may be associated with improperly designed electrodes or cabinets that have sharp edges.

The risk of burns must be broadened to include burns that occur because of the passage of electrical current through resistant tissue, causing heat to be produced by joule heating, and those burns that occur because of chemical reactions at the surface of the body, caused by the passage of current through the tissue electrode interface. Current-induced thermal burns are not at all unlikely in those cases where the electrical current used is at a frequency above that which evokes sensation, and current densities can easily be so great as to cause severe tissue damage without any electrical shock effect. For example, the problem of current-induced thermal burns has been particularly acute in the use of the electrosurgical unit. This unit employs currents of the order of 1 mHz and levels that approach or exceed 1 amp.

The subtle effects of chronic exposure to subthreshold currents and fields have been studied, producing much controversial data. It is not an area that I would judge as significant to your studies, but I feel you should be aware of the possible risks of chronic exposure to subthreshold currents and fields.

The device that performs improperly and gives wrong information is a risk factor that normally is not considered. The device may be out of calibration, have an altered frequency response, or have developed an inappropriate nonlinearity. The use of such a device is considered a risk to the patient because it may lead to a wrong conclusion concerning the subject's condition. In clinical medicine, a missed diagnosis because of incorrect performance of a device is a risk whose consequences may be every bit as great as those of electrical shock, burn, or fire.

THE EFFECTS OF ELECTRICAL SHOCK

The host of effects that electrical current can cause cover the whole gamut of severity. For example, a subject may experience little or no sensation upon exposure to an electrical current. On the other hand, electrical current may cause a subject to lose consciousness, to suffer severe tissue burns, or to die. Shock sensation can be mild as a gentle tingling at the point of contact; or, the subject may experience a much more general shock, producing a tetany of muscles that would make it impossible for the person to break contact with the energized circuit, thus holding the respiratory muscles in a contracted or immovable state so that breathing becomes impossible. The more general shock may also cause such severe muscle contractions that bones may be broken. Electrical current can cause fibrillation of the heart or other irregularities of cardiac rhythm, burns of the skin and deeper tissue, or set off a convulsion.

The outcome of an electrical shock is dependent on a number of factors. As Table 1 indicates, an important factor is the intensity of the shock, usually expressed in terms of the current (for example, in milliamperes or amperes).

Table 1

Effects	Electrical Current
Threshold of sensation of electrical shock	1 milliampere
Failure to let go	10 milliamperes
Interruption of respiration	20 milliamperes
Ventricular fibrillation	60 milliamperes to 4 amperes
Defibrillation of the heart	4 amperes to 10 amperes
Prolonged respiratory paralysis and severe burns	above 10 amperes

The values in Table 1 should not be taken as clearly defined thresholds for these phenomena, but rather as approximate orders of magnitude at which these responses will occur. There are many other factors that affect the subject's response to a given current.

Ventricular fibrillation is a state of chaotic disorganized contraction of the heart muscle fibers that causes the blood to stop circulating. In human beings, ventricular fibrillation rarely spontaneously reverses itself, and is usually fatal unless treated promptly. It may seem paradoxical that an electrical current greater than that which causes fibrillation can be less lethal, but in fact, this is the case in the current ranges that are identified with defibrillation of the heart. This fact is exploited in devices called cardiac defibrillators, which are used to reinstitute cardiac activity.

Duration of the shock is almost equally as important as shock intensity because it governs the amount of energy imparted to the body. Moreover, many excitatory phenomena provoked by electrical currents have an inverse relationship between the intensity of the current and the duration of the current necessary to evoke a response. For example, a short shock may cause a muscle or a nerve to respond only if the current is significantly higher than that current which will excite the nerve at a longer duration. The contact area also plays a role in that it frequently determines the magnitude of current that will result upon contact. In general, a large area of contact implies a lower resistance for the shock circuit, and therefore, generally, a greater current.

The pathway of the shock through the body cannot be overlooked. A current pathway that does not include the heart, for example, a pathway from one leg to the other, is much less likely to result in cardiac irregularities than a current pathway that travels from one hand to one foot, traversing the torso and going directly through the heart.

Frequency or waveshape of the electrical source has a marked bearing on how a shock affects the subject. In general, the body is less sensitive to high frequency electrical currents than it is to low frequency currents. Studies on the sensitivity of the heart to varying electrical frequencies show that the frequency at which the lowest electrical current will cause ventricular fibrillation is at approximately 60 Hz. This frequency has been chosen for electrical power distribution, and thus is widely available.

The temporal relationship of the shock to periodic phenomena in the body sometimes will determine whether a detrimental effect will result. For example, very short electrical currents, those of the order of a 10th of a second or less, must occur at a specific portion of the cardiac cycle, frequently referred to as the vulnerable period, if they are to cause ventricular fibrillation. Undoubtedly, there are other physical or psychological factors that influence the outcome of electrical shock. It is not outside the realm of possibility that emotional or other factors generally relating to the physical or mental well-being of the subject affect whether a response to an electrical shock occurs.

Thus, in many cases it is difficult to predict the precise outcome resulting from an electrical shock. Time does not permit me to go into depth in this area, but any of the effects of electrical shock that seem paradoxical become much more understandable if these complex interactions are considered in greater detail.

METHODS OF PROTECTING SUBJECT

A general philosophy for protecting the subject from electrical risks can be summed up simply: The intention of any protective measure is to restrict the current that can pass through the subject or to limit the voltage that can be applied across the subject.

There are numberous approaches for enhancing the subject's safety, for example, because inadvertent current pathways so frequently involve the passage of electrical current to ground, the subject should be protected by insultation materials or isolated from grounded surfaces. This reduces the possibility that the subject will become a portion of an unintended current pathway to ground.

Electrical safety is enhanced when subject-connected circuits for either the acquisition of physiologic information from the subject or for applying stimuli or monitoring currents to the subject are isolated from the ground. When such circuits are not ground referenced, the possibility of inadvertent currents to ground through the patient are markedly diminished.

Proper electrical distribution systems also contribute to overall safety. In this country, our electrical distribution systems are overwhelmingly of the grounded type, that is, one of the power-supplying conductors at each outlet is grounded. There are valid reasons why these systems have been developed, though at first glance it may seem that greater safety would be afforded by a system that has no intentional ground connections. Suffice it to say that the choice of a grounded electrical distribution system is predicated upon factors that contribute to the reliability of the system's performance.

Since we have to live with the grounded distribution system, it is necessary to follow proper procedures for installation and maintenance. It is particularly important that receptacles be wired consistently so that the grounded conductor can always be identified. Let me comment parenthetically that the grounded conductor is that power conductor that is a ground potential. It should not be confused with the third conductor in a power cord, the green wire, which serves as a grounding conductor to which the cases and chassis of electrically-operated equipment are connected. The differentiation may seem subtle, but even in devices operated on electrical distribution systems that do not have any of the power conductors grounded, it is still important in improving safety to ground the cases and chassis through the green grounding conductor. When wiring polarity of receptacles is carried out consistently, devices can be plugged into that system with a fair degree of confidence that the devices will be connected in a manner that will ensure the least leakage current.*

Effective grounding may be considered an extension of the idea that distribution systems must be properly installed. I draw specific attention to this as an important factor in the safe operation of a system. Devices that are properly grounded reduce the subject's risk of exposure to adverse and inadvertent currents. Effective grounding includes not only ensuring that the cases or chassis of electrically operated equipment are grounded, but also that other conductive materials in the region in which equipment is being used are sufficiently interconnected to one another and to ground. When these precautions are taken, potential differences or sources of electrical current that could become a risk are harmlessly shunted away from or around the subject.

Good design is a keystone to building greater electrical safety. In particular, a design that reduces leakage current and minimizes the chance of failures leading to energization of the accessible surfaces or subject-connected leads, reduces the risk of shock or adverse effects.

Great strides have been made in recent years as attention has focused on what was presumed to be an electrical shock problem in hospitals. While studies concerning leakage current were never adequately documented to provide convincing proof that leakage current was causing the "electrical shock" problem, the attention focused on this area nevertheless stimulated improvement in the design of medical equipment, so that now the leakage current in vast numbers of medical devices has been reduced to levels that are considerably lower than those considered achievable in past years. On the average, chassis leakage current from these devices is less than 100 microamperes, often as low as a few tens of microamperes, and leakage currents from subject-connected leads are routinely well below the commonly accepted limit of 50 microamperes. These values are commonly accepted as upper limits on leakage current from patient-related devices. Other equipment is permitted a maximum leakage current of 500 microamperes.

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*Leakage current is usually low current that normally occurs in the operation of electrical devices and in pathways other than the intended current-carrying circuits. It emanates from the chassis of the equipment and is conveyed harmlessly to ground by the grounding conductor in the power cord.

In addition to system and device design and implementation, there are various specific devices that are frequently introduced into the system with the aim of increasing electrical safety, for example, local power distribution systems that are isolated from any connection from ground. Such systems limit the magnitude of currents associated with failures in plug and receptacle combinations or in power cords. They provide an added feature in that they permit a faulty system to operate at relatively low risk without interruption of power until an orderly transition to alternate equipment can be made or until completion of repairs. Many codes and standards require that these isolated power systems be used in anesthetizing locations, since these systems are generally not prone to producing sparks that could ignite inflammable anesthetics. More recently, awareness of the significance of improving electrical safety for the benefit of the patient and attending personnel has increased. This has led some to use isolated power systems in special care areas in other hospitals and at other locations where it is felt the need for improved electrical protection may be necessary.

Ground fault circuit interrupters are capable of sensing small current flows to ground that are outside of the intended pathway, while at the same time remaining insensitive to large magnitudes of current flowing in the intended pathway. There is a widespread application for this device; in fact, the ground fault circuit interrupter is required by electrical codes for use with electrical services supplying swimming pools, outside receptacles, and bathrooms in newly built homes. The disadvantage of using ground fault circuit interrupters is that on detection of a fault, power to the device is interrupted, and this interruption may be untenable in certain circumstances.

The detection techniques used in ground fault circuit interrupters have recently been extended to another class of devices, resulting in what is known as a ground fault monitor.

This device can be interposed in the power line to indicate, either visibly or audibly, when leakage current is above the prescribed level. Thus, the ground fault monitor is able to inform the user when limits have been exceeded, without interrupting the circuit. Other protective devices, which are much less commonly used, are those that monitor the continuity of grounding conductors, thus assuring that adequate grounding of equipment is present to minimize the risk of exposure to energized surfaces.

Two additional items also contribute greatly to the safe use of electrical equipment. One is an effective regular program of inspection and preventive maintenance of equipment. This practice is most effective when it is directed not only towards a product's safety and protective features, but also when it takes into consideration the performance characteristics of a device or system. Failure of a device to perform properly may put the subject at risk if, for example, because of faulty equipment, the subject must be retested in a program in which there is some inherent risk in the testing procedure. Second, the user should be educated in the proper use of the device and be knowledgeable of its safety features and its risks. The importance of this second item in enhancing the safety and integrity of electrical devices cannot be overstated.

EXAMPLES OF TYPICAL DEVICE OR SYSTEM PROBLEMS AND SOLUTIONS

I would like to cite some problems or failures that have a marked impact on the safety of devices used in everyday settings, for example, in the home. Power cords and plugs often are abused. They lie across floors and are walked on. Carts and tables are wheeled over them. The cord is used to withdraw the plug from the receptacle. People trip over the cord and put a strain on both the equipment and the plug. Therefore, it is no wonder that many safety problems arise from failures in power cords and plugs. Problems of this nature are avoided most easily by a regular program of preventive maintenance in which the condition of line cords and plugs is inspected for cracked insulation, to ensure that strain reliefs have not been abused or are not inadequate, and to ensure that wiring at the plug is correct and tight.

Users should insist that equipment be supplied with cords that are strong enough to withstand abuse. It is important for the user to know that the cord should not be used to remove the plug from its receptacle. Plugs should be examined to ensure that ground connections have not been cut off. Plugs molded onto the line cord have a history of broken grounding conductors within the plug assembly leading. There is widespread skepticism in the medical community concerning the integrity of molded plugs. The siutation is changing as designs improve, but the performance of molded plugs must be watched closely.

A class of devices has evolved within the past five years known as hospital grade plugs and receptacles. These plugs and receptacles have been produced especially to withstand abuse, particularly with respect to the integrity of the grounding connection. In general, these devices should be used when there is great concern about the electrical safety of equipment. These plugs and receptacles are compatible with ordinary parallel-blade units, and are generally identified by the presence of a green dot conspicuously placed on the surface.

The innocuous little device frequently referred to as a cheater, an adapter that enables a two-pronged receptacle to receive a three-pronged plug, is one of the most insidious culprits in seriously degrading electrical safety. Frequently, it is implemented with a wire pigtail that must be fastened securely to a grounded point. The screw that holds the coverplate on the receptacle is often taken as the point to which the cheater is to be connected, but unfortunately, the coverplate is not always connected to ground. The result is that frequently grounding is not achieved when these devices are used. The obvious solution is to avoid the need for these cheaters by installing proper receptacles that have the third contact for grounding. Any receptacle should be installed properly and then checked immediately to ensure that it has been wired properly. It should also be tested with one of the simple tension testers that are now available to ensure that there is adequate holding force for each of the plug's prongs.

Extension cords are another problem, along with their closely related cousin, the adapter cord. When I say adapter cord, I am referring to those "short extension cords" that consist of a plug and a connector mounted on a short piece of wire that permits non-standard plugs to be connected with standard receptacles or vice versa. Extension cords and adapters introduce another set of contacts in the electrical pathway that is subject to failure, and at least doubles the probability of a problem occurring.

If they are excessively long, extension cords also add resistance to the power circuits and grounding conductors and may reduce the safety and effectiveness of the device. The solution is to avoid or ban the use of extension cords. The use of extension cords could also be reduced by providing long power cords on electrical devices. Occasionally, adapters may be necessary but they should be considered as electrical equipment and be included in any inspection program to ensure that hidden damage has not occurred.

Failures that would normally not occur occasionally show up in devices that expose the subject or the experimenter to potentials on subject-connected leads. Selection of well-designed equipment is crucial to minimize this risk.

It may happen that too many grounds will occur, especially when an effort is made to assure that everything is well-grounded. In this situation, redundant grounding pathways may lead to a complete circuit that might include equipment contacting the subject. If there are strong magnetic fields in the area, especially at power line frequency, and these magnetic fields course through the area contained within the loop formed by this closed ground pathway, currents known as "ground loop currents" may be induced in the ground system. These can create, at the very least, interference in signals being monitored and, under extreme conditions, they can expose the subject to potentials that would not otherwise have occurred. To avoid these problems, grounding should be carried out carefully. In general, the problem can be minimized if devices are singly grounded. This is usually accomplished through the grounding conductor in the power cord. Where it is possible, grounding conductors from individual equipment should come to the same point or to the same electrical branch circuit rather than going to widely disparate points within the area. Except in unusual circumstances, no wire should be added to tie equipment together.

CODE STANDARDS AND REGULATORY MECHANISMS INTENDED TO ENHANCE ELECTRICAL SAFETY

There are a number of standards and codes that users can turn to for guidance, and which manufacturers, whose overall aim is to raise the safety level of equipment and systems, make use of in equipment design. Many of these standards and codes are produced by a consensus process; that is, a process that is intended to ensure that all parties affected by the proposed standard will have an opportunity to review and to contribute to its development. I will briefly mention several regulatory bodies involved in developing standards and codes.

The Association for the Advancement of Medical Instrumentation (AAMI) is a group that produces a number of voluntary standards for a variety of devices that are applicable in medical and related fields. The organization has broad representation, including device manufacturers, clinical and biomedical engineers, physicians, and nurses. One standard the AAMI has created that is probably of the greatest interest to you is the standard that sets safe limits for leakage currents in health care devices.

Another well-known and widely respected agency that produces codes, standards, and recommendations is the National Fire Protection Association (NFPA). Historically, the NFPA has concentrated on activities intended to reduce risk from fire. However, the NFPA has increasingly embraced other areas, such as electrical safety. It is not surprising that the National Electrical Code, one of the NFPA's most visible byproducts, is an outgrowth of its objective to reduce risk from fire. The National Electrical Code prescribes wiring methods which, among other things, are intended to minimize fires caused by poorly designed or implemented electrical systems.

The NFPA has numerous other standards including one presently under development that would propose methods for the safe use of electricity in health care. This document, commonly referred to as NFPA 76B, when adopted, will provide a guideline likely to be used well beyond the walls of health care institutions. Many of the principles on which it is based can be adequately carried over into human research facilities. The codes of the NFPA are widely adopted, although the NFPA itself is not a code-enforcing authority. For example, adherence to the National Electrical Code is not monitored by the NFPA, rather, the code is adopted by local enforcing authorities or by other governmental agencies and is applied by force of law.

There is an intensive international effort to produce standards. This effort is largely the work of an organization called the International Electrotechnical Commission (IEC). The IEC has produced a vast array of standards intended to ensure the uniformity of products on an international level. The IEC is presently refining a comprehensive document for medical devices.

Underwriters Laboratories (UL) is widely recognized as an organization that contributes to the safety of devices and appliances. In general, the UL does not write codes and standards for other groups, it formulates them for use in assessing equipment submitted to the UL by manufacturers who want to obtain the right to place the UL label on their products. Standards formulated by the UL are reviewed by persons representing diverse interests and a broad audience outside of the UL organization before they are applied to devices under examination.

The UL has earned a good reputation for promoting safety in electrical products. Up to this time, many of the specialized devices used in research laboratories have not carried the UL label. There are several reasons for this. In the past, manufacturers of these devices have not found it necessary in the competing marketplace to seek UL listings to promote their products. In addition, obtaining UL listing entails a considerable expense on the part of the manufacturer and any significant model change means that the product must be resubmitted. In the future, we are likely to see more devices, particularly those used in the medical field, that carry either the UL label or display evidence that the device has been screened by a process similar to the Underwriters service or has been judged to be in conformity with standards being developed by the Food and Drug Administration. Individual investigators will have greater assurance that devices have been built with an eye toward safety, as well as toward efficacy or desired performance.

CONCLUSIONS

The foregoing is a brief overview of the various factors that are important in assessing the safety and performance of electrical systems. The topic is an immense one, which cannot be adequately addressed in this paper. The safe use of electrically-operated devices is the result of a combination of a number of factors, including safe design, implementation, and knowledgeable use of equipment. To the extent that these factors are considered in the development and use of electrical equipment, the risks encountered will be minimal.

Discussion Summary

Discussants questioned whether it is necessary to use three wires in grounding rather than two, since the neutral and the ground are joined together in the ground system. A hypothetical situation was constructed in response to this question, in which the grounding is accomplished at the service entrance point. Next, it was assumed that there are two devices adjacent to each other, each fed by separate branch circuits, and each having its frame grounded to its own neutral.

One device is a high current device, with a heater element that draws 25 amperes. The 25 amperes of load current goes back to the neutral, and the resistance in the neutral results in a voltage difference between the chassis of that unit and the point where the neutral is grounded back at the transformer.

Next, it was assumed that the other device has no load current. Hence, its chassis is essentially at the same potential as the point where the neutrals of these two systems are grounded. However, because of the drop in the neutral feeding of the device with high current, there may be a significant voltage difference between the enclosures of the two devices.

A separate grounding conductor intended to provide grounding for the chassis is run to prevent large load currents from flowing into those conductors, and to obtain a near equality of the potentials of the chassis. Thus, there is a practical reason for using three wires in the wiring system rather than two.

Participants also discussed the problem of separate power supplies in a single area. One particular concern voiced is the possibility of power from different service panels converging in an area where grounding points are of different potentials. Discussants considered the merits of equipotential grounding, a system designed to prevent the occurrence of just such a situation.

The concept of equipotential grounding has been a key issue in the development of the NFPA 76B impending standard. Basically, this standard would place limits on the potential differences permissible within the vicinity of a patient or subject. Provisions in the standard also call for a certain amount of interconnectedness of the grounding systems that derive from separate panels, to ensure that potential differences will be minimized.

Participants said that equipotential grounding should be an important consideration in the design of any facility because it is necessary to limit the potential differences on the grounding system. Besides creating risks in terms of subject safety and device performance, potential differences on the grounding system cause interference in many physiologic recordings.

EPA HUMAN STUDIES PROGRAMS

CLEANS/CLEVER System Approach

John H. Knelson, M.D.
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The concept of controlled environmental research using human subjects is not new. I was given the mission about eight years ago by a predecessor agency of the EPA, the National Air Pollution Control Administration, to find out the technological accomplishments in this field of research.

The result of my inquiries led to the development of the CLEANS/CLEVER project now underway at Research Triangle Park. CLEANS is the acronym for Clinical Evaluation and Assessment of Noxious Substances; CLEVER stands for Clinical Evaluation and Verification of Epidemiologic Research.

The CLEANS facility, adjacent to the medical center complex on the campus of the University of North Carolina, consists of two large exposure chambers with an adjoining computerized physiologic data acquisition system. Using these computer-controlled chambers, researchers can expose human subjects to the same conditions of polluted air that are present in urban and rural areas.

The CLEVER project consists of two mobile laboratories, each containing equipment identical to that housed in the stationary CLEANS facility. The mobile units collect and evaluate clinical data from epidemiologic field studies.

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Both CLEANS and CLEVER are capable of closely controlling environmental conditions such as light, temperature, humidity, and airflow, and both are computer equipped to measure a variety of human cardiovascular and pulmonary functions. The intent of these two types of laboratories is to link findings obtained from field research with findings from controlled clinical studies.

To study the effects of airborne pollutants on human health and welfare in a controlled laboratory setting, we select, with specific criteria in mind, human research subjects and manipulate these subjects and their environment in a predetermined way. We define the dose, the pollutant, and the exposure regimen, and then we decide which physiologic, metabolic, neuroendocrine, hematologic, and psychophysiologic end points we intend to study. Once these end points are defined, we study the responses of individuals who reside in a manipulated environment for a set period of time.

By manipulated environment, I mean one that either simulates urban or rural conditions, or one that is very clean in terms of particulate counts and gaseous concentrations. In such an environment, factors such as temperature, humidity, light intensity, and sound levels are controlled to predetermined values.

What kind of machinery do we use in our experiments? How do we get our data? How do we process our data? How do we validate it? How are we assured that we are doing what we think we are doing, both in terms of manipulating the environment and in acquiring the physiologic or biologic data that we think we are acquiring? These questions form the subject of this discussion.

During the formative years of the CLEANS/CLEVER program, I visited every laboratory conducting environmental research that I could identify. One of the first places I visited was Dr. Kerr's laboratory. Dr. Kerr impressed upon me that a study design that depends upon external environmental conditions is subject to many problems.

Some of the early experiments at Ranch Los Amigos were designed to study and document the physiologic functions of people residing in a clean environment. To gather data on polluted air, the researchers depended on the ambient, supposedly polluted, air obtained from the laboratories' urban location. Although there were certain merits to that experimental design, the research was subject to the vagaries of prevailing weather conditions. I decided not to contend with the kind of problems such as experimental design involves, and instead would design a laboratory that had the capability of stimulating in a highly reliable, predictable, and well-characterized fashion the atmospheric conditions that occur in our urban environments.

A design of this type is a leap from the real world into the stimulated laboratory world. You pay something for that leap, but you gain better control of your experiment. Over the years that we have been developing the EPA Human Studies Program, the substantial advances made in air quality assessment have diminished the price we pay for simulating the real environment. The advantages, however, of being able to control our experiments have remained the same.

Another impression I received from the laboratories I visited was that most investigators were able to acquire a tremendous amount of data, but they really did not have the logistic capability to thoroughly examine the data they acquired. It was clear that if the data were computerized and preprocessed, it could be examined as it was acquired. Moreover, preprocessed data is much easier to analyze than thumbing through stacks of line printer output in an attempt to make sense out of the data after the experiment is finished. The practicality of preprocessed data plus the advances in air quality measurement and the advances in the technology for simulating environmental conditions helped us decide to computerize and automate our environmental control system.

It has become a cliche to have a complete feedback loop, independent of human intervention, to control sophisticated environmental simulations. We thought we could gain better control of our studies and construct a much more sophisticated environmental simulation if we used high-speed computer equipment capable of constantly adjusting the environment for us as the feedback loop worked. To this end, we evolved an automated physiologic data acquisition system and an automated environmental control system.

A sine qua non of clinical research is to control the research project so effectively that the risk to the human participant in an experiment becomes vanishingly small. If you depend on extensive mechanical support systems to provide a simulated environment, an interjection of many safety systems into that environmental support machinery provides layer after layer of redundancy for safety's sake.

If you depend on manual control of your mechanical support system, it will probably work reasonably well, but a manual system does not have the reliability of a system that processes many data points per second. Such a system gives you real-time appreciation of what the analyzers are showing in controlled environmental laboratories.

The program concept of human studies began in 1969 -- during the period of Earth day, the end of the Vietnamese war, and the general unrest on the nation's campuses. At that time, it was difficult for a federal agency, even a benign one such as the National Air Pollution Control Administration, to communicate effectively with university administrations. However, we were well received at the University of North Carolina, and our reception by the University is essential to any success that we may ever attain.

Because the CLEANS/CLEVER program would take a long time to get started, we decided to install a less sophisticated mechanism that we could use right away. We built an acrylic chamber that has been the source of much valuable data. In a few months we were able to design and successfully conduct an experiment with reasonably well defined sulfuric acid aerosols. The chamber has become a valuable pilot laboratory for debugging experiments; it will be moved into the bigger, more expensive facility.

We spent roughly two years preparing design specifications for the research facility. The contract we awarded included research, development, design, and construction. Research and development was such a large fraction of the overall cost that we decided that the construction of duplicate laboratories, in terms of hardware costs, was not inordinately expensive. Consequently, two laboratories, identical as far as physiologic data acquisition is concerned, were installed side by side. The use of two laboratories doubles the throughput of the entire facility at relatively little additional cost.

Physiologic Data Acquisition System (PDAS)

Our physiologic data acquisition system provides us with a variety of information, much of which concerns cardiopulmonary functions because that is the subject we study most often. We receive information either directly from the subject, or from instruments attached to the subject. The data measured by the instruments, such as gas concentrations and flow rates, travels through analogue signal channels outside the chamber into buffers and multiplexers, and then into the computer system where they are digitized.

Communication lines allow the computer to control certain aspects of an experiment without human intervention. One of the simpler tasks is time of use calibration of the instruments. This task is not quite as simple, for instance, as control of the treadmill during exercise stress testing. Developing software for exercise stress testing (i.e., exercise electrocardiography) proved more difficult than anticipated, so we decided to write the algorithms for the simpler tests (spirometry and body plethysmography) and apply what we learned from those tests to the development of the exercise stress testing programs.

If necessary, we can operate the facility without the computer. In the event that the computer is inoperable for a predictably short period, we can continue an expensive experiment by acquiring our data offline until the computer is functional once again. It would be inconvenient to insert offline data into the computerized data, but I think I would prefer to do that rather than throw away the whole experiment.

Our PDAS is not totally independent of the human operator. The digital data base processed by the computer supplies the operator with information he needs to decide whether to intervene or to allow the system to operate independently. The software can prompt the operator to perform certain tests, or it can perform the tests automatically. During the course of an experiment, direct visual communication with the subject inside the laboratory is maintained by a closed-circuit television camera. In addition to an electrocardiogram attached to the subject, there is an oscilloscope readout of the subject's pulmonary functions. The readout is displayed on two CRT screens as either digitized waveforms or as alphanumeric information.

The use of this equipment allows for human intervention in our highly mechanized system. For example, when a simple spirometry test is conducted, within a few milliseconds after the forced expiratory vital capacity maneuver is completed, a digitized waveform shows on the CRT screen. Identifying hatch marks indicate where certain software decisions were made. If the operator is not satisfied with the point where the pattern recognition algorithm indicates the expiration occurred, he can capture the identifying mark with the cursor and move it to where he thinks expiration actually occurred. When the operator moves the cursor, the computer will create a file that has both the original digitized data and the derived data for the waveform as it was defined by the computer. Next to that file another file is created containing the new information calculated on the basis of where the new cursor mark was placed.

The nerve center of the PDAS is what we call the functional keyboard -- a panel of 25 numbered pushbuttons (five rows of five buttons). By manipulating the keyboard, we can call up a variety of software programs. We can choose any part of a program by simply pushing the right number on the keyboard. Whenever any test is designed that we want to include in our system, we can write the appropriate software for that test and insert it into the entire algorithm.

When the keyboard panel is not lighted, the buttons cannot be pushed. When the panel light flickers, the buttons are ready to be pushed, at which time the panel becomes solidly backlit. The solid lighting indicates to the operator that he may proceed with whatever routine he has chosen. If the operator wants information on spirometry, the system does not compel him to go through the entire program of spirometry in a predetermined sequence. If desired, the operator may choose certain components of the program, such as forced inspiratory volume or forced vital capacity. Thus, the keyboard provides for human control of the PDAS; it gives us the option of deciding when, and to what extent, to perform a given test.

Another facet of this system is the alternative to either throwing out or keeping data -- in other words, a way of saving data we suspect might be incorrect so that we can check it later. When we want to save data of this type, we put a special flag on it by hitting the "poor data" button on the keyboard. If desired, we can enter free text in a file that might say, for example, that the subject coughed halfway through his FVC and we are uncertain whether or not the data has been changed.

The other portions of the software package are not yet written. The system is really infinitely expandable and alterable because it is totally software dependent. Expansion is limited only by our imaginations, what we decide we want to do, how much core we want to buy, and how many new programs we plan to write.

Environmental Control System

A class 100 clean room is an artificial, arbitrary engineering requirement, but it is one that would warm the cockles of most investigators' hearts. We decided that a class 100 clean room would be our objective for our environmental control system.

We can achieve, relatively easily, class 1,000 clean room conditions. Such conditions may not be clean enough for assembling microcircuits, but they are clean compared to the clean air that people breathe most of the time, and class 1,000 conditions are a nice control for us.

The outside air is prefiltered. To properly control temperature, we must use both heating and cooling in series. To maintain good control of relative humidity, we dry the air and then reinject the desired amount of water vapor. The air comes in through the top of the controlled environmental laboratory, where diffusers provide reasonably laminar flow from ceiling to floor. The air is exhausted out through the perforated floor of the laboratory, through several banks of high-efficiency particulate filters. In addition, the air is filtered through activated charcoal.

We have several levels of safety control as far as our environmental system is concerned. The delivery of pollutant gases into the air flow system is through low pressure lines, so if any loss of integrity of that system occurs inside the building, we are not dealing with a high pressure system coming off the supply bottles.

There are, at various points in the system, critical orifices through which you cannot push air any faster than a certain flow determined by the size of the orifice. This puts a mechanical ceiling on the level of pollutant that we can put into the laboratory. The actual makeup of the laboratory air is determined by the pollutants injected into the air flow just proximal to the axial vane fan; therefore, pollutants are churned up and well distributed.

For any particular circumstance, the volume of air flow is a function of the damper setting, the speed of the fan, and the pitch of the impeller blades on the fan. When these three factors are adjusted simultaneously, they will determine the air flow through the laboratory.

Allow me to back up a moment to point out the difference in the two laboratories that I mentioned earlier. They are identical with respect to gaseous air pollutant capability -- specifically, ozone, sulfur dioxide, nitric acid, nitrogen dioxide, and carbon monoxide. In one of the laboratories, we are installing the aerosol generating and monitoring capability. The air flow for one of the chambers had to be a little bit different than the air flow for the other in order to accommodate the aerosol capability.

The aerosol generators can put any water soluble substance into the air stream. The number of particles and the size of the particles is determined by the concentration of the solution supplying the nebulizer, the solution flow through the nebulizer, and the air flow through the nebulizer. These three parameters determine the mass concentration in the chamber and the particle size distribution. The composition is determined by whatever is put into the solution. That is why, for instance, we do not bypass the hepa filter if we get it down to clean conditions. Then, once most of the unwanted particles are eliminated from the airstream, we bypass those filters to filter out all of the aerosol we introduce in the system.

The solenoids either opened or closed, and the length of time spent in the open mode or in the closed mode, determines the concentration of pollutant gas in the chamber. These are hydraulically-operated, compressed air solenoid valves.

A high-limit alarm allows the operator to intevene, if necessary. Even before the alarm goes off, the operator can monitor the actual analogue output of the sensors. Because he knows the relationship between analogue outuput and pollutant concentration in the laboratory, the operator is able to find out whether or not the predetermined pollutant concentration is actually in that laboratory.

If the computer does not maintain the predetermined concentration of pollutant, the operator is able to intervene by changing potentiometer settings or by manually overriding the computer. In the case of either computer malfunction or computer crash, we think the operator can successfully maintain the predetermined concentration in the controlled environmental laboratory so that the experiment can continue. In the event that this is not possible, we have made provisions for a single button to be pushed by the operator which will abort the experiment and purge the chamber. The button turns on the fan and opens the fusable link dampers. Within a few seconds the chamber is completely evacuated of that particular pollutant concentration.

We are most concerned about data quality control. Health Effects Research Laboratory personnel are responsible for and are in charge of all experiments. However, because we do not have adequate engineering support staff in our laboratory to conduct these experiments, we have a rather substantial operating and maintenance contract with Rockwell International. We keep a close watch on the laboratory environments that are maintained by our contract personnel. Conceptually and administratively we monitor the data quality control for both the physiologic data acquisiton system and the environmental control system in the same way.

From time to time, though, an independent audit is conducted by a third party and gives EPA a report. From that and from our observation of the operation and maintenance of the environmental laboratory, we will produce a data quality report from time to time.

I would like to touch on some of the main aspects of the data quality control, and some of the philosophical points in data quality control. Very simply, we constantly make mechanical status checks. For instance, with regard to the air flows, we know that in order to properly maintain the environment, air flows at certain points must be within certain limits, and that is checked constantly. For temperature and humidity control, we take corrective action to make sure that dampers are accurately set and that the integrity of the circuits is sound. Finally, all the analyzers are frequently calibrated with NBS referable standards.

As far as the pollutant system is concerned with respect to data quality control, we measure gas concentrations, obviously, but we also look carefully at the gas flow rates past certain points. If they are not within certain bounds, we know that even though gas concentrations might be what we think they should be, there is something wrong with the system. Solenoid positions obviously have to be maintained in a certain configuration in order to produce the gas concentrations we want.

Data quality control of the physiologic data acquisition system is somewhat more complex because it is more difficult to make sure the computer is giving information that closely corresponds to the data that are actually coming from the subject. One of the ways to assure the reliability of computer information is to compare it with canned or known input. Canned input is synthetic data; for example, an ECG simulator is used or spirometry data are mechanically produced. Such data are the same day after day. Anytime you wish to check whether the numeric data flashed on the screen are the same as they were the day before, you can run the canned, or known, data through the computer.

We use physical calibration just as anybody does in any laboratory, but we are also striving to achieve a high quality of electronic time of use calibration. This is accomplished by using the computer, which can detect any deviation in electrical signals. If one or five milliwatts is put through, a certain signal is obtained from the computer. Split signal redundancy analysis is yet another approach. This permits us to split a given electrical signal and run it through both of our computers. If the computers are working properly, the same answer is obtained from both of them.

If we get different answers, we may not know which one is right, but at least we know that a problem exists. Trend analysis is simply the intelligent and knowledgeable human operator watching the computer output for suspicious changes in the data. This is a very soft kind of data quality control, but the computer output of good trend analysis information probably will tip us off to something.

Algorithm error analysis is, of course, applicable to any algorithm, regardless of whether the algorithm is operating a chamber or whether it is processing data obtained from a piece of physiologic equipment. This type of analysis provides us with built-in range checks. We know, for example, that vital capacity should not be 15 liters or 500 cc.'s. If a data bit is identified as unbelievable by our definition in the algorithm, then the data is flagged so that we can examine it.

I would like to conclude with a quick overview of where we might be going with this. We have completed the first 30 subjects of ozone adaptation in clean air, and we hope the experiment will reveal some answers about differences in lung performance as it relates to the length of time a subject has been breathing ozone.

We are very concerned about nitrogen dioxide and other environmental stresses, such as heat, in conjunction with various pollutant stresses. By January 1978, we should have a good capability of generating aerosols, and by July 1978 we should actually be able to generate and monitor them with online computer control.

Finally, our staff is now preparing the comprehensive program plan that will describe how this facility will be used for the remainder of this decade. We know what research capabilities we have and we know the priorities and needs of the Environmental Protection Agency. We encourage your participation is this preparation process. Your ideas, your thoughts, and your proposals are a national resource. We invite you to join us as correspondents or, on occasion, as visiting scientists.

SPECIAL CONSIDERATIONS AND APPROACHES IN ENVIRONMENTAL CLINICAL RESEARCH

Moderator: Philip Bromberg, M.D.

Introduction to Panel Discussion

Philip Bromberg, M.D., Moderator
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I should like to disregard the typical question of what is response and what is disease. Dr. Bates, who unfortunately is not here to defend himself, suggests that response is disease, and that the burden of proof is on those who claim that response is not disease.

I should like to proceed to the question: What does one measure as the effects of the agents that we are examining? How do we measure them? When do we measure them?

The first thing that is measured is gross toxicology, for example, excess mortality during air pollution academics. After that, the researcher looks at the causes of the symptomatic and mortality effects that have been produced.

Perhaps the first approach is to look at lung function. As researchers probe deeper into the functions of the lung, they develop new concepts of how the lung works, and produce more and more elegant and sophisticated tests of lung function. These studies are applied to man, as well as to animals.

Then, newer indices of lung actions are developed. When we look at these new indices, the way they are studied progresses from gross (e.g., the effect of ozone in fairly large concentrations on airways is epithelium slough) to refined, to extremely elegant.

In more refined studies, the researcher can look not only at the gross destruction of the epithelium, but also at the rate of turnover of epithelial cells, which is a more refined index of the death rate of epithelial cells.

Finally, the researcher can begin to study even more elegant indicators, such as how permeable the airway epithelium is to materials deposited in the lumen of the airways. This permeability overall may be affected by the so-called mucous layer, although it is not clear that the mucous layer is really a continuous layer. Because it is an epithelium, the airway lining is characterized by "tight junctions" between the epithelial cells. In many tissues, these are known to limit the permeation of both the small and large molecules.

Some evidence indicates that noxious agents, gases, can affect the intactness of the tight junctions of the respiratory epithelium and its permeability characteristics. The latter effects allow materials to be deposited in the airway, where they penetrate the deeper layers of the epithelium and act upon smooth muscle vasculature and mast cells.

What exactly are we to measure and how are we to measure it? These are questions that are subject to continual development and refinement. The highlight of this kind of approach is always mechanisms. We are not just interested in gross effects, but also in the mechanisms that produce these effects.

I think that to answer this question coherently, governmental regulatory agencies, such as the EPA, which is responsible for developing concrete air quality standards, must be concerned with mechanisms. Even though this conference focuses on human studies, we should not limit our attempts to define air pollutant levels to such studies. Our studies must be accompanied by an attempt to understand the mechanisms that produce the effects.

Another difficult topic is the independent variable. We have already heard that there are many problems pertinent to the identification and measurement of the independent variable. There are multiple agents. There is, of course, the ordinary dose effect relationship. There is the problem of timing--when, after exposure, should one look for effects? How long should exposures be? What about tolerance? What kinds of interactions are present between external noxious agents; interactions with other pharmacologic agents; interactions with physiologic stimuli, such as exercise; interactions with temperature, humidity, and particles? These questions give rise to so many permutations and combinations that, to perform really pertinent experiments, I think one must have a particular objective in mind--not merely a broad hypothesis.

For example, a researcher ought to examine the mechanisms of how a particular noxious agent works, and consider what type of experiment can be devised to obtain more information about it, rather than attempt to answer a question such as "Is this gas noxious?"

Another major problem is the subjects we use in our experiments. Whom should we choose as our subjects? Should our subjects be healthy, or should we be looking at subjects who have some type of disease? Disease, as well as health, is difficult to characterize in human beings.

Finally, what are the effects of informed consent on human subjects? Does the subject's knowledge of what effects to expect influence his symptoms, and consequently, the test's so-called objective findings? Real problems can arise from this element of the equation. Again, I plead that researchers should think mechanistically rather than simply be satisfied with the observation of one effect or another.

Now, the panel and the audience may or may not agree with everything I have said. I would like each member of the panel to have a chance to make a statement of his own. Then we can have some discussion after each member of the panel has had an opportunity to talk, and follow up with a general discussion.

Statement

Robert Frank, M.D.
Department of Environmental Health
University of Washington

I want to respond to some of the things Dr. Bromberg mentioned. My personal philosophy regarding clinical research can be stated as follows: First, clinical research can be directed toward understanding phenomena (Dr. Bromberg referred to this); that is, toward providing a basis for an observed response. Second, clinical research can be applied to describing dose-response relationships for a particular agent.

Both objectives are important, particularly the latter. Dose response relations affect standard setting, which in turn can significantly affect society.

I also think the investigator engaged in the latter type of clinical research should be prepared to discuss the biological significance of his results. At the very least he should attempt to assign some weight to his results. If he fails to do this, then other scientific investigators perhaps ought to take up the task, because if they do not, the task will be taken up by non-scientists.

As Dr. Bromberg indicated, it is entirely possible that the particular functional parameter under examination -- the so-called dysfunction the researcher may have observed -- may, by itself, be readily tolerated or quickly reversible. Alternatively, it may be insignificant, but have important secondary effects. Dr. Lippman

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has stated, for example, that the transient bronchoconstriction associated with exposure to irritants may in turn lead to increased deposition of inhaled particles, which obviously has implications for biological dosage.

But, if the investigator suspects that a dysfunction has significant secondary effects, then he should state his hypothesis and test it. At the moment, I think there are a number of so-called positive findings in clinical research that have received more attention than they deserve.

There may be some reasons for this. No one likes to profess that the product of his work, the effect he has observed, has only questionable or minimal importance. To do so means monumental inattention to the researcher's study and a loss of funds.

A word about functional testing. We rely rather heavily on measurements of ventilatory function and respiratory mechanics. There is good reason for this reliance. In the past these measurements have been extremely useful and revealing, but we must remain resourceful and be prepared to move beyond them, to recognize when testing our hypothesis may demand additional techniques.

For example, Lippman has shown with sulfuric acid aerosol administered to donkeys that in the presence of little or no changes in respiratory mechanics, there may be significant depression of mucociliary clearance.

I am somewhat surprised to notice that in assessing changes in function that are due presumably to reflect bronchoconstriction, many of us still depend exclusively on a ventilatory test that requires a maximum inspiratory maneuver. Years ago, Nadel showed that a maximum inspiration can abolish, at least temporarily, bronchoconstriction. Also years ago, Arend Bouhuys showed that a partial expiratory flow-volume effort, which avoids this danger of abolishing reflex bronchoconstriction, can be more revealing than a flow-volume effort begun following maximal inspiration. Perhaps this is a test we ought to use more often.

Furthermore, when we start experiments involving ultra-fine or accumulation mode irritant aerosols, as for example sulfuric acid, we ought to emphasize tests that assess small airway function. After all, such particles are most likely to land in the periphery of the lung. This suggestion, at least in my own experience, is borne out by studies on guinea pigs exposed to submicrometric aerosols. Their dynamic compliance can be affected more often than their total flow resistance. It is not easy to assess small airway function. The tests are often time-consuming and their interpretation may be open to debate. Such tests can become distracting in studies in which the functional changes may be occurring rapidly.

In my judgment, the measurement of closing volume has not been too revealing. Also, the forced expiratory flow rate at 25% of vital capacity has a rather high variance so that subtle changes in small airway caliber may elude detection by this means.

Dynamic compliance, which may be useful for detecting unevenly distributed changes in small airways or parenchyma, is another test that is difficult to accomplish. It requires an esophageal catheter and a well trained subject. It is not always easy to control what has to be controlled, that is end-expiratory lung volume and tidal volume, when the subject breathes at different frequencies. Perhaps we should experiment more with the helium oxygen techniques developed at McGill University. McFadden found this technique to be quite revealing in his studies of exercise-induced bronchoconstriction. One problem may be the time required to perform it.

Presently, my belief is that we ought to focus more attention on what I term the "hyper-reactive subject"; in other words, a subject who is otherwise normal and with no known underlying chest disease. For the sake of discussion, I will accept Amdur's definition of a hyper-reactive subject as someone whose functional change during exposure to a pollutant is at least three times greater than the average group response. Amdur reviewed the literature and noted that a number of investigators working in the field encountered one or two subjects in their group who suited this definition. For the moment we will exclude allergy as the basis for hyper-reactivity.

Several questions might be asked about this type of subject: Is the hyper-reactivity typical of the subject? That is, if I observe an exaggerated response on Monday to a pollutant, will it be present on Tuesday, Wednesday, Thursday, and one month later? Does it have some plausible or identifiable mechanism? For example, is it a matter of internal dosage?

You may recall the observations of researchers at New York University years ago suggesting that the pattern of particle deposition in the periphery of the lung is determined in great measure by morphometric factors. Just as the aerodynamic characteristics of an aerosol influence its rate and site of deposition, so may airway and alveolar dimensions and ventilatory pattern. All of these biological factors can vary considerably within the normal population. Such variations among lungs, and particularly within a lung, may become very important once lung disease has been established. There are likely to be variations in the distribution of ventilation within a diseased lung, leading to local "hot spots." Morphological factors of this type are likely to impose differences in dosage, among or within lungs, over long periods of time.

I wonder how much differences in bronchoconstriction among subjects inhaling drugs such as acetylcholine or mecholyl may be due to differences in the deposition rate or dosage.

An alternative explanation is that the exaggerated response may reflect an altered or increased responsiveness to the same fixed dosage. In his recent work on dogs, Nadel found that following ozone inhalation, there was a clear-cut increase in the bronchoconstriction in these animals produced by parasympathomimetic drugs. This hyper-reactivity reached a peak about 24 hours after the ozone inhalation and thereafter receded. In this instance, neurophysiological changes in function produced by exposure to ozone, apparently led to hyper-reactivity. He noted, too, that infection may produce the same result.

Functional or inflammatory factors of this type are likely to impose differences in dosage over limited periods of time. As I see it, if we could identify and understand the basis for hyper-reactivity, we might be able to predict who among the population is at greatest risk. The rewards might be especially high for occupational settings, wherein the workers at greatest risk might be identified before any impairment of health occurred. I think it is a worthwhile hypothesis toward which research efforts should be directed.

To move to another subject, it is probably a truism that we ought to combine pollutant exposure with other forms of stress during clinical experiments. This is particularly true when we administer realistic concentrations of pollutants to healthy human subjects. The most obvious concurrent stress is exercise. Studies including both these variables, that is, exposure plus exercise, have been well exploited by Drs. Bates and Horvath. It is probably true that the more vigorous the exercise, the more likely the effect on the response to the air pollutant. Some of the reasons for this phenomenon are known. The increased ventilation that occurs during exercise causes a greater amount of the pollutant to be introduced into the respiratory system per unit of time, and the increase in instantaneous flow rates that occurs during exercise is associated with a reduction in the scrubbing efficiency (fractional uptake) of the upper airways for soluble gases and particles. This is particularly true when the subject switches from nose to mouth breathing during exercise.

In addition, there is probably some alteration in the sites of transfer of these gases and particles in the lower airways. For example, when a subject ventilates at high flow rates while inhaling a particle of sulfuric acid, as during exercise, the pH of the particle at the instant of impaction in the airways is probably lower than during quiet breathing. This difference in pH may be the result of two phenomena. First, the particle may be less hydrated during exercise when there is less time for it to absorb water (before impaction) and therefore, less time for the water to dilute the hydrogenion concentration. Second, there is also less time for any chemical transformation or neutralization of the particle by ammonia in the upper airways.

There are other forms of stress that have not been adequately explored. Recently, Dr. Horvath has begun combining heat with exposure to pollutants. We have not, to my knowledge, rigorously studied the effects of a combining cold and a pollutant, especially when a soluble gas is combined with a droplet aerosol. Certainly, one of the impressive features of epidemiologic studies is that sudden changes in ambient temperature may overwhelm the effects of pollution.

Finally, an approach that I think is potentially as rewarding as any other is to study the effect of psychological stress on response. We have not yet begun to design appropriate psychological stresses for this purpose, and I have no idea how to proceed. It is possible that noise might be an effective co-stressor.

My last point is really designed to evoke a not-always-friendly response. In clinical research, we are beginning a generation of experiments in which multiple pollutants are administered simultaneously for several hours. The ostensible purpose of these experiments is to see if the combined effects of the simultaneously-administered pollutants are addictive, synergistic, or conceivably, antagonistic.

I have misgiving about a number of these studies as follows: Unless there is a plausible chemical or physical basis for interaction among the pollutants that will cause them to form some new, presumably more irritant species or end product, or unless there is a plausible argument why two or more pollutants are likely to affect the same biochemical or physiological function, or at least affect separate functions that are interdependent, the results of such studies are likely to be disappointing and ambiguous.

Experiments of this type are extremely complex in design. They require repeated observations on the same individual to establish whether synergism, et cetera, has occurred. I have been impressed with the variance in the responses of subjects to the same pollutant on different occasions, as well as the variance in the functional parameters that have been tested.

The researcher is likely to end up with the product of these several errors, which makes it extremely difficult to detect all but the most dramatic effects. I could readily support an attempt to study the biological consequences of interactions among sulfur dioxide, ozone, and some droplet aerosol. The analytical chemist tells us that there is a reasonable likelihood for a heterogeneous reaction among these agents with the formation of an irritant small particle.

But I would be less enthusiastic about mixing agents like sulfur dioxide, nitrogen dioxide, and carbon monoxide. Unless I am mistaken, these three gases do not interact and their sites of effect are by and large different. I would seek the rationale for such a mix and would not be satisfied to learn that it is "because all three gases are found in polluted air." Our resources are too limited for that sort of luxury.

Discussion

DR. HAZUCHA: Dr. Frank mentioned hyper-reactive subjects. Certainly, you have to find out how to identify and study these subjects. But from my experience with testing 20 or 30 subjects, we usually find one or two who do not react at all. To get a true picture of the response, we have to identify not only hyper-reactive subjects, but the hypo-reactive subjects as well.

DR. FRANK: I couldn't agree with you more. Again, I am speaking as a member of a society concerned about protecting people. It is true that you may learn as much about this phenomenon of hyper-reactivity by pinpointing what it is about the subject that protects him, or dampens the result, as you do by identifying what it is that exaggerates the response.

DR. CAVENDA: You have not mentioned repeated tests (other than the fact that the subject reacted on Monday, Tuesday, Wednesday, Thursday) to determine if, over a period of time, a subject might be tested for changes in response. For instance, a subject might experience anxiety the first time he engages in a new activity defined by the testing procedure. This may produce a response that is the result of the effect of psychological stress, which may diminish as the subject grows accustomed to performing the activity on a continuous or chronic basis.

DR. FRANK: I did not emphasize it, but in speaking of hyper-reactivity, I posed the question: "Do subjects respond the same way when tested repeatedly?" I think you can define "repeated exposure" as you choose.

I would agree that anxiety can influence response. We ought to test this notion as an hypothesis. I think anxiety is a particularly important factor when you are testing a highly sensitive population, such as asthmatics.

DR. KNELSON: We specifically take into account the problem that has just been raised. We do not test for intra-subject variability as Dr. Frank suggested, but at the Health Effects Research Laboratory we try to control it as a variable.

One of the most important parts of our experimental design is the training period, the habituation period of all the subjects prior to the onset of the experiment. This is the last hurdle that the test candidate has to pass before he can become a subject for experimentation. During this period, we find out if the subject is capable of becoming a reasonable habituated, trained individual in the environment we expect him to participate in for a few hours or a few days.

We not only control for differences in response (we call it "training effects") the way I have described, but we also test for its persistence. Do the data on Monday differ from those on Tuesday, Wednesday, Thursday, and Friday? No, we have found that they do not.

The first experiment we ever conducted here was with carbon monoxide. In that particular case, we designed a double-blind, crossover study that specifically addressed the question of whether the subject's performance was different on Friday than it was on Monday. I think the idea of testing this as a hypothesis is very interesting. I would suspect that we would have considerable amount of variance.

DR. FRANK: I happen to think that many responses are characterized by a considerable amount of variance. You can define an experimental circumstance in such a way that you say, "I will eliminate variance by dropping all subjects who do not satisfy my definition of conformity."

But in doing that, you may exclude some significant proportion of the population. I wonder if in some way -- it might be very difficult -- we shouldn't begin looking at the excluded proportion of the population as well.

DR. HIER: The variance within a subject could be so-called stochastic variance, too; that is, the subject's response could vary randomly from day to day. To account for random daily variation, we take repeated measurements and average out that kind of variability. If you want to introduce a specific variable, for example, anxiety, you introduce particular conditions that might exacerbate anxiety in one setting or another, so that it becomes a cross-condition effect.

But I am concerned that variability from one time period to the next is not being ascribed to strict experimental conditions -- that subjects are being subjected to more or less anxiety, to more or less training effect. But even after you control for all these variables, you still must contend with stochastic variability. The important thing is to take repeated measurements.

DR FRANK: I would like to respond to Dr. Hier. In the typical experiment, one or perhaps two measurements of fuctional parameter are taken, and then an animal or human subject is exposed for a period of hours, followed by one or two measurements taken during or at the end of the exposure. My impression is that this procedure is extremely thin ice on which to characterize: one, the baseline function; and two, the changes that may be imposed by the stimulus you are applying. We very often stretch the data beyond the weight it can really support.

DR. BENIGNUS: By "thin ice," do you mean the paucity of measurements taken?

DR. FRANK: That is right, because the few measurements we make do not truly characterize the response during the period under study.

DR. BENIGNUS: Two measurements are not very much.

DR. OTTO: Just a quick follow-up on what you are saying. I agree very much with the comments about how to deal with statistical variability, but there are problems with using a repeated measurement design. For instance, if you are dealing with a chemical agent, you may be considerably limited by a repeated measurement design because the chemical's cumulative effect may thwart your attempts to obtain responses at the baseline level. In short, responses may be modified by cumulative effects.

You may decide to wait three or six months to take another baseline measurement, but by that time numerous factors far beyond our control have changed--the temperature, the climate, the individuals' home lives, or the subjects may no longer be attending school. These are particularly strong variables that we have had to face when dealing with the student population.

DR. FRANK: These are highly complex experiments, and unless you have a hypothesis that you can test plausibly, and unless you pay real attention to this problem of describing the functional parameter before and after you intercede, you are going to end up with ambiguous data, which often happens in this field.

DR. OTTO: The importance of the initial finding may be much greater than later findings because the subject's tolerance to the test substance may change. The strength of the response is going to change and become much weaker.

So, I am not so much worried about the importance of the initial changes that are observed. In fact, sometimes with carbon monoxide, we suspect that response changes may be an effect that occurs very early at very low levels -- that the organism is able to adapt almost immediately, say, within 20 to 30 minutes; and, if you do not catch the response as it occurs, you miss it forever. It is a real problem.

Statement

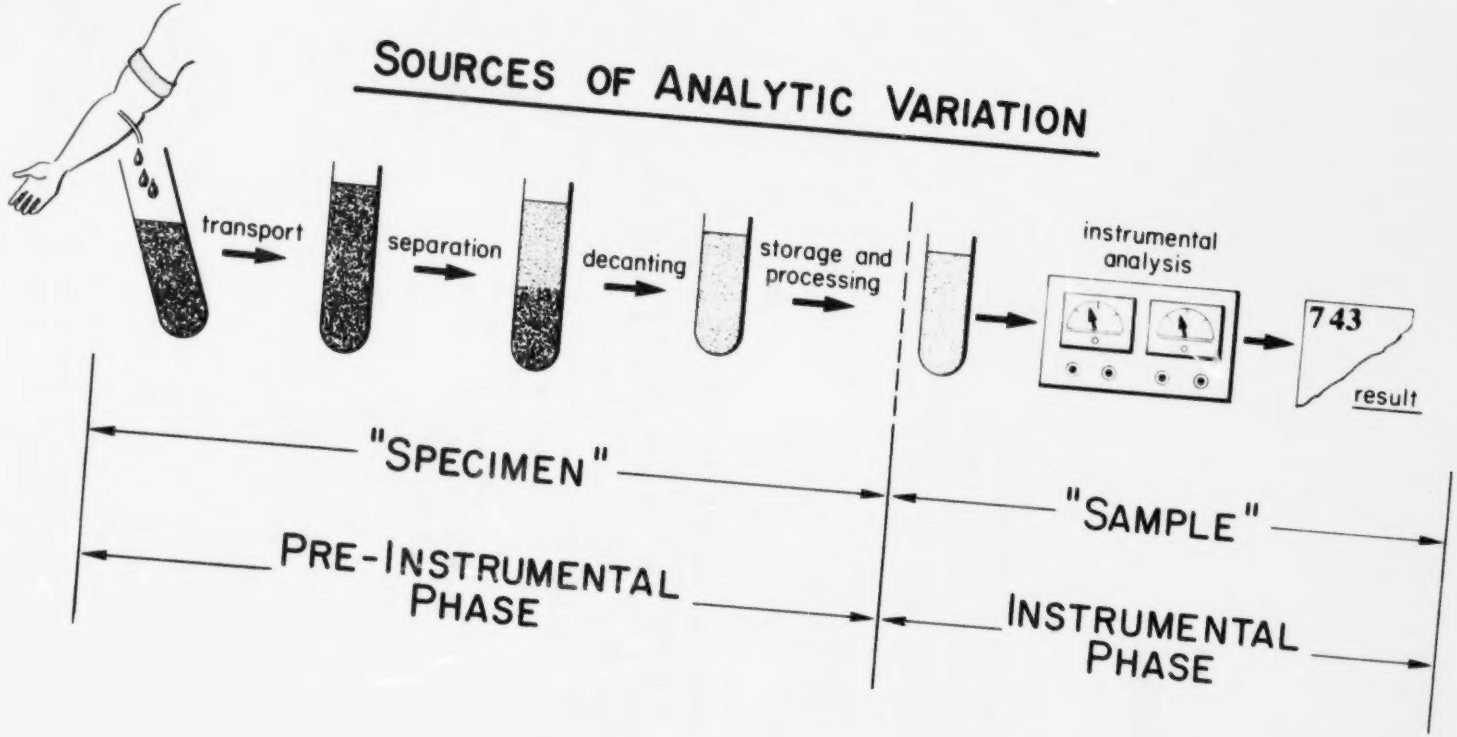
Bernard E. Statland, M.D., Ph.D.
Department of Pathology
University of North Carolina

I would like to discuss the general problem of intra-individual variation of laboratory results. Intra-individual variation is the variation in results that one would note over time in one individual. This problem should be of great interest to all investigators studying the effects of environmental stresses on humans. So often investigators use mean changes in a group of individuals rather than looking at a person as his own control. Since many of these stresses of the environment will evoke a significant change within an individual, but not for a group as a whole, it is pertinent to understand the expected sources of intra-individual variation. As soon as we have an understanding of the sources and magnitudes of the expected intra-individual variations, we will be better equipped to handle the experimental problem.

The major sources of intra-individual variation of laboratory results (and also most other variates which we measure in individuals) can be grouped into three types:

1. Analytical variation
2. Variation due to preparation of the subject
3. Variation due to temporal considerations when obtaining a specimen

Figure 1 schematically presents the source of analytical variation. The analytical variation can be divided into two types:



SOURCES OF ANALYTIC VARIATION

transport
separation
decanting
storage and processing
instrumental analysis
743
result
"SPECIMEN"
"SAMPLE"
PRE-INSTRUMENTAL PHASE
INSTRUMENTAL PHASE

Figure 1

the preinstrumental sources of analytical variation and the instrumental sources of variation. The preinstrumental sources of variation in results determined on a specimen of serum would include the venipuncture procedure itself, the filling of the tube(s) of blood, the transportation of the whole blood specimen, the centrifugation step, the variation occurring while the serum sits on the clotted cells, the decanting of the serum supernatant, the storage of the serum specimen, the freezing and thawing of the specimen, and the processing of the specimen prior to the specimen entering the instrumental station. The instrumental sources of variation in the case of laboratory results obtained on a serum sample include the dispensing of the specimen, the uncertainty in the temperature during which the analysis is performed, and the spectrophotometric uncertainty, etc. Most approaches of quality control of the analytical variation are truly only monitoring the instrumental phase and not the preinstrumental phase of the analytical procedure. Obviously, the intra-individual variation in laboratory results obtained on an individual will always include the analytical sources of variation. The analytical sources of variation will be the sum of the within-batch and the batch-to-batch variations.

The second major source of variation is that due to the preparation of the subject. Subject preparation includes all those factors done to the individual or by the individual independent of the pathological process (or environmental stress) that one is investigating. Examples of such factors are prior exercise, previous diet, ethanol ingestion before specimen collection, posture of the subject, and tourniquet application time.

The effect of exercise on serum enzyme values can be appreciated from the information seen in Figure 2. In this figure, we are depicting the percent change from baseline values in four subjects at various hours after a one hour exercise stress. The four subjects were males who underwent a 1 hour game of paddleball. At 1 hour, 5 hours, 11 hours, 19 hours, 29 hours, 43 hours, 53 hours, and 67 hours after the stress, specimens were obtained from these subjects. The activity values for the enzymes creatine kinase (CPK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (AP) were determined on the serum specimens. The values were compared with baseline values (those obtained prior to the exercise stress). As noted in Figure 2, the mean creatine kinase values were 120% above baseline at 11 hours after the stress. The AST and LDH values also were elevated significantly. CPK, AST, and LDH are all enzymes present in muscle. Alkaline phosphatase is not present in muscle to any great degree. This enzyme showed very little change after the exercise stress.

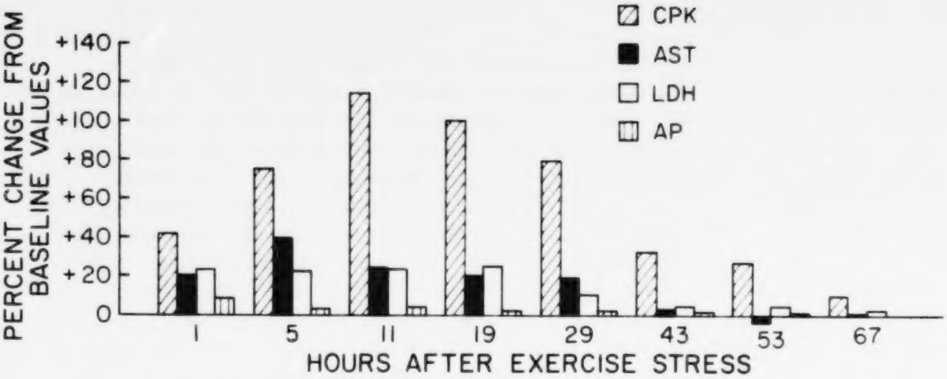


Figure 2

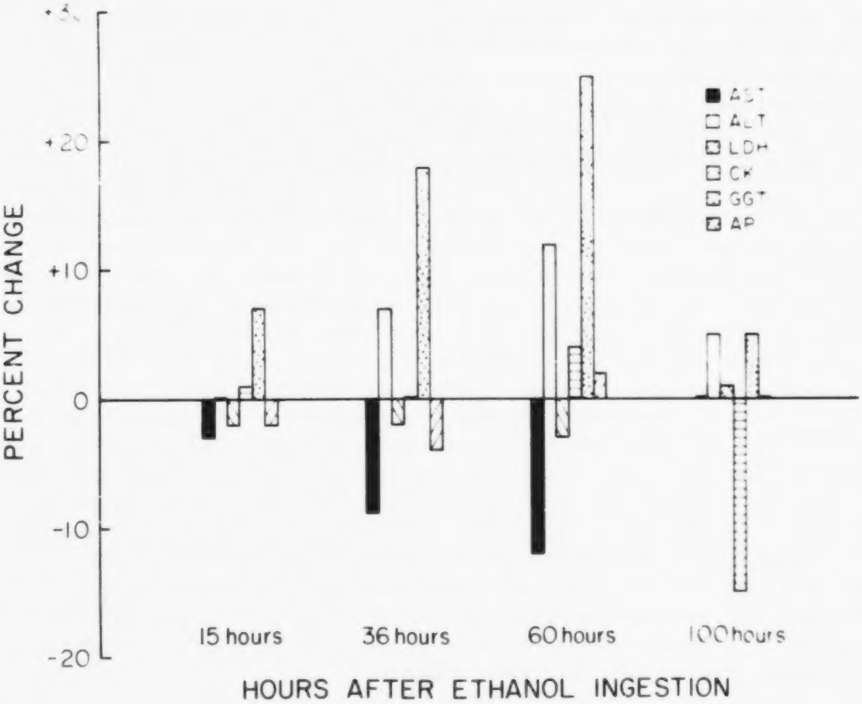


Figure 3

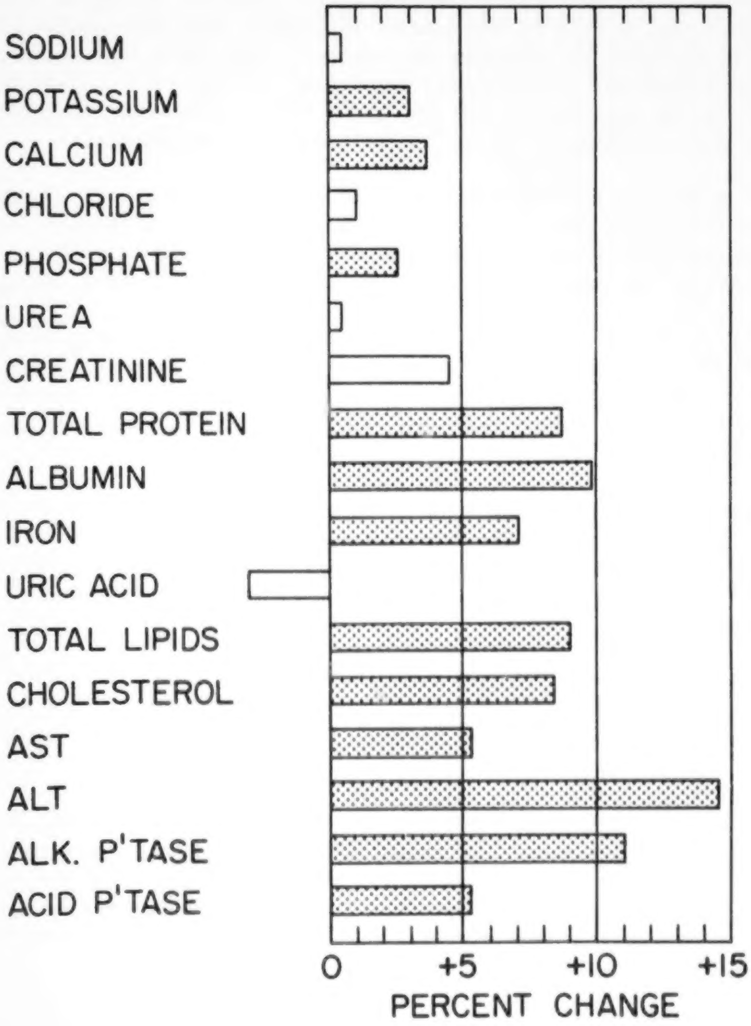
We evaluated the effects of ethanol ingestion on nine healthy subjects. The subjects had baseline values determined for the serum enzymes AST, ALT, LDH, creatine kinase (CK), gamma glutamyl transferase (GGT), and AP. The ethanol stress consisted of 0.75 grams of ethanol per kg of body weight ingested on three separate evenings. At 15 hours, 36 hours, 60 hours, and 100 hours after the third evening of ethanol ingestion, specimens were obtained and determined for the enzymes depicted in Figure 3. The most impressive change was noted for serum GGT. The mean increase in GGT was approximately 25% at 60 hours after ingestion.

We examined the effects of posture on a number of serum analytes in 11 healthy subjects. These healthy subjects, all male aged 21 to 24 years, had blood obtained both in the supine position (lying horizontally for one-half hour) as well as in the erect position (standing for 15 minutes and sitting 1 minute before venipuncture). As noted in Figure 4, the serum proteins, analytes bound to proteins, and enzymes were significantly increased. The bars in Figure 4 represent the percent change going from the supine to the sitting position. In the case when such a change was significant, the bars are stippled.

The third major source of intra-individual variation is that variation due to the effect of time of specimen collection. The temporal considerations can be divided into the within-day (hour-to-hour) and day-to-day changes. I will concentrate on the day-to-day changes.

Figures 5, 6, 7, and 8 represent the concentration values for serum thyroxine, serum cortisol, serum triglyceride, and serum cholesterol in each of four healthy subjects. The subjects are labeled number 3, number 5, number 7, and number 8 in these figures. Blood was obtained at the same time of day after the subjects were in the sitting position. The posture and tourniquet application time were standardized. As noted in these figures, the intra-individual variation for thyroxine was greater than the inter-individual variation. However, for the constitutents serum cortisol, serum triglyceride, and serum cholesterol, the intra-individual variation was much less than the inter-individual variation.

The relationship of the intra-individual (within subject) to the inter-individual (subject-to-subject) variation can be appreciated for the values of alkaline phosphatase activity in the serum of four healthy subjects. Figure 9 presents the values obtained on each of 6 days during a 10 day period for four healthy volunteers. It is obvious that the subjects maintain their values for alkaline phosphatase in a very narrow range during the course of the study.



SODIUM
POTASSIUM
CALCIUM
CHLORIDE
PHOSPHATE
UREA
CREATININE
TOTAL PROTEIN
ALBUMIN
IRON
URIC ACID
TOTAL LIPIDS
CHOLESTEROL
AST
ALT
ALK. P'TASE
ACID P'TASE
0
+5
+10
+15
PERCENT CHANGE

Figure 4

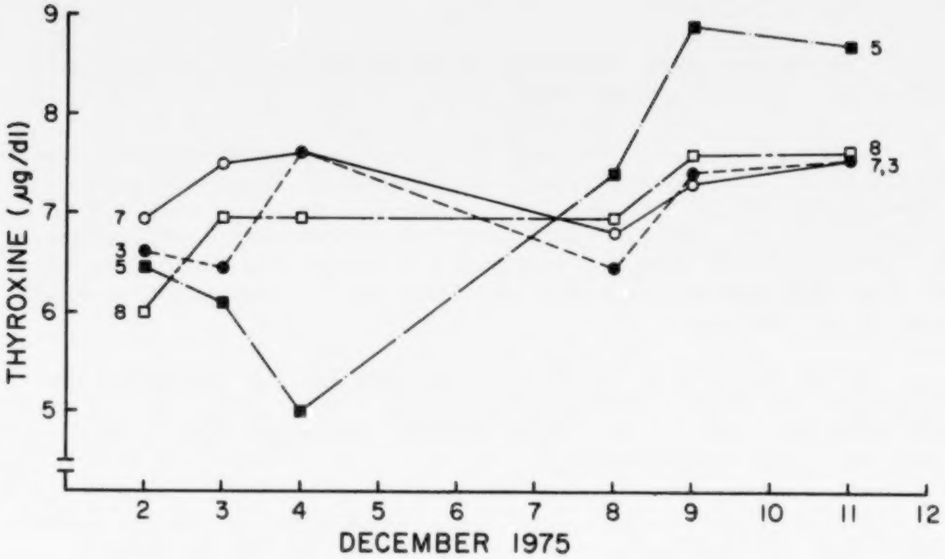


Figure 5

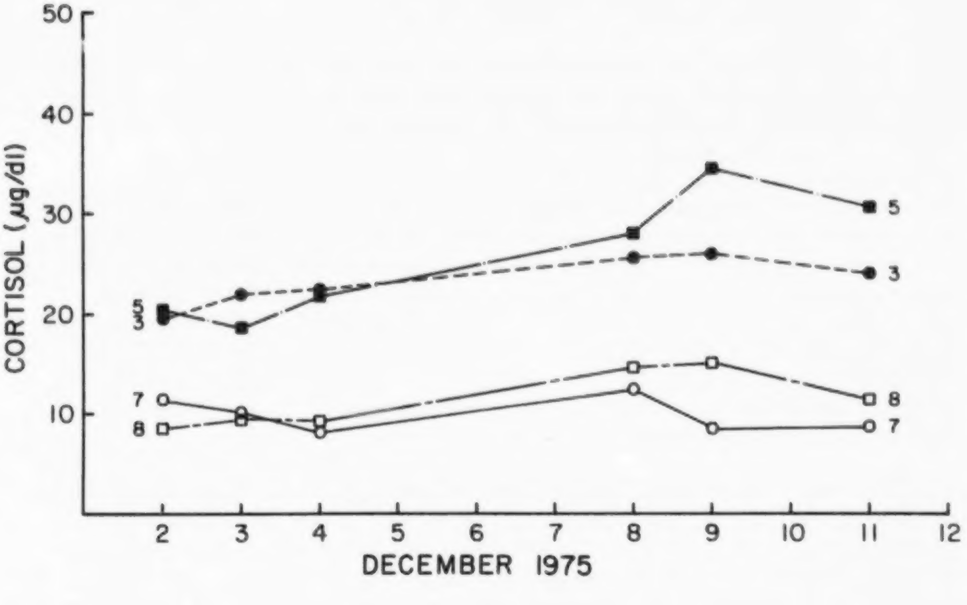


Figure 6

Note that we are using arbitrary units rather than international units for alkaline phosphatase.

Figure 10 depicts the ranges for alkaline phosphatase for each of fourteen individuals studied over 10 days. Specimens were obtained at 8:00 in the morning. They were analyzed in one batch at the conclusion of the study in order to decrease the magnitude of the analytical variation. In such a manner, we would only have to deal with the within-batch variation and not the batch-to-batch analytical variation.

Figure 11 shows analogous information for the concentration values of the serum complement C4 values. Once again, we see that the individual maintains a much narrower reference region than does the group of individuals.

The conclusions drawn from our studies thus far on the intra-individual variations or serum constituents are the following:

1. Under conditions in which the analytical variation and the variation due to the preparation of the subject are minimal, the intra-individual variation is often much less than the inter-individual variation of mean values.

2. When the intra-individual variation is much less than the inter-individual variation, it does make sense to use a subject's baseline values as his own control.

When electing to use a person as his own control, there are certain issues that must be taken into account. The first issue is deciding on the appropriate biological model of time-series that a value is expected to follow. Two major models have been composed: the homeostatic model and the random walk model. Figure 12 illustrates the homeostatic model. In this model it is assumed that a subject has a mean value below and above which all values should fall. The variations from the mean are taken into account in order to compute a prediction interval within which the next value should fall. In Figure 12, we are examining four values of serum iron in a healthy subject. The fifth value should be expected to be the mean of the four. The width of the prediction intervals is dependent upon the standard deviation of the previous four values.

In the random walk model (see Figure 13) the next value in a series of values should most likely be the most previous value. In Figure 13, we are looking at the same four serum iron values seen in Figure 12. The prediction interval, however, is 8.2 to 21.1 for the 95% prediction interval as compared to 10.7 to 24.6 for the homeostatic model. It is quite obvious that one must choose a model of biological time-series before being able to evaluate the width and the location of the prediction interval.

When using a person's values as his own control, the analytical variance plays a very important role in the width of the prediction interval. The relationship of the analytical variance to the biological variance is depicted in Figure 14. This figure represents the relationship of the percent increase in intra-individual variation due to analytical error to the ratio of the analytical variance over the biological variance. When the ratio of the analytical variance to the biological variance is 1.0, one would expect a 42% increase. When the analytical variance to the biological variance is 4.0, the expected increase is greater than 120%. It had been recommended that the analytical variance to the biological variance ratio be no greater than 0.25. In this latter case, the percentage of increase would be approximately 12%. Such a guideline might be very important in prospective clinical studies as well.

In conclusion, I have discussed the various sources of intra-individual variation that we as clinical chemists must deal with. However, the intra-individual variation has much wider applicability than just to clinical chemistry. It should play a role in monitoring a number of variates including blood pressure readings, respiratory function tests, and other parameters that are followed over time. Since more and more investigators are using a subject's previous values to evaluate the effect of various stresses, the elements going into the intra-individual variation should be noted.

The work I have presented here has been done in collaboration with my colleague Dr. Per Winkel who is presently at the Finsen-institutet in the Department of Clinical Chemistry in Copenhagen. This work has been supported in the main by the Danish Research Council, departmental funds from the University of Minnesota, and departmental funds from the University of North Carolina, Department of Hospital Laboratories.

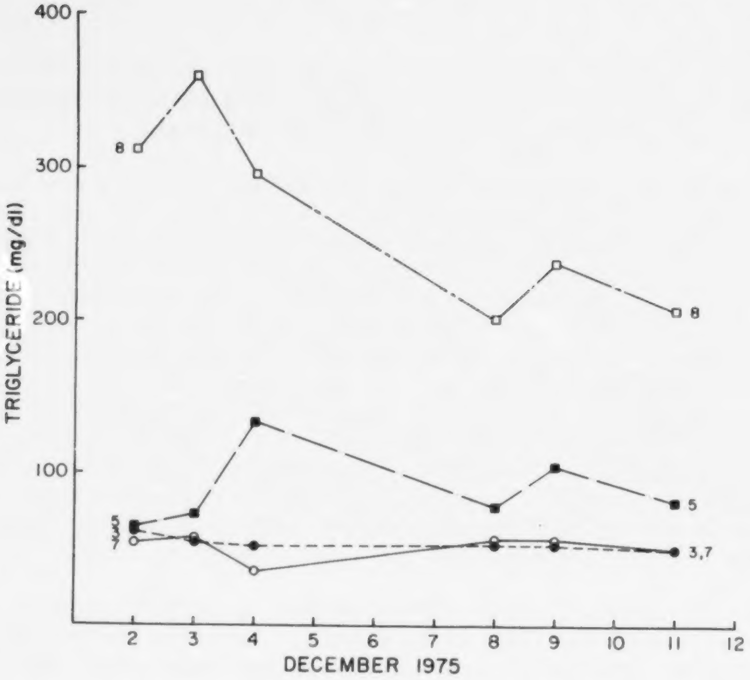


Figure 7

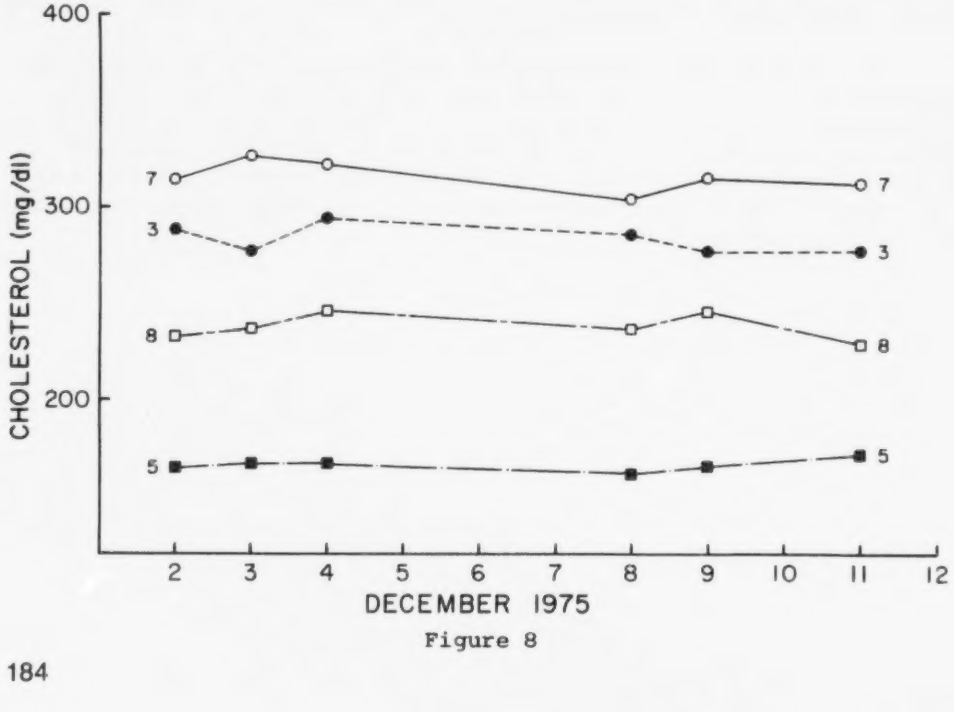
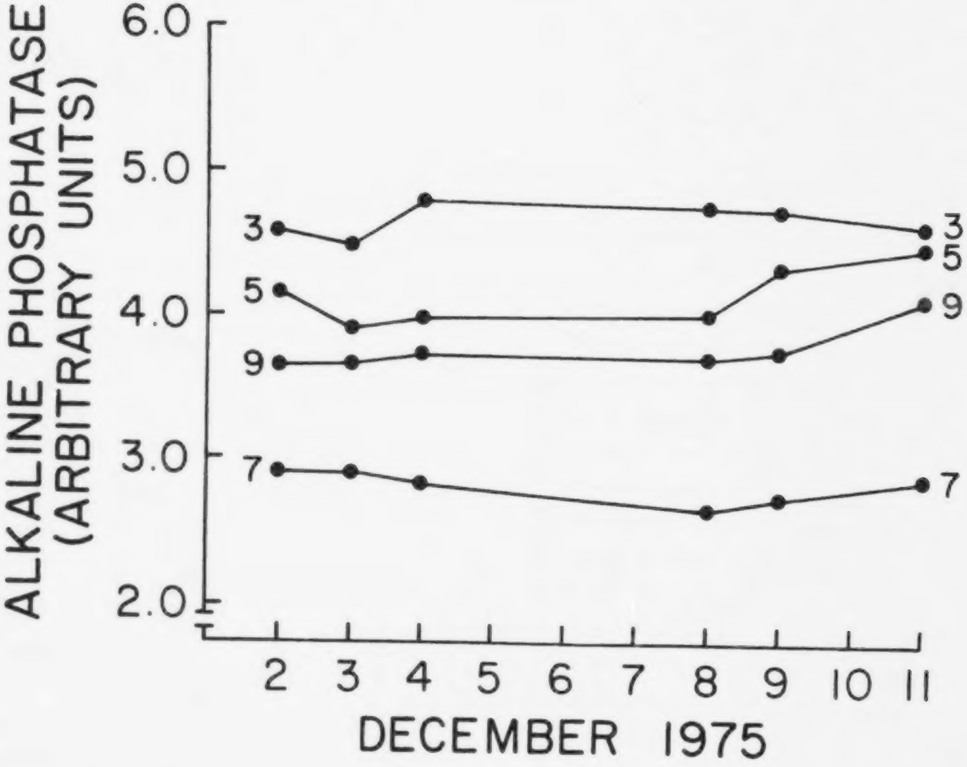


Figure 8


ALKALINE PHOSPHATASE
(ARBITRARY UNITS)
6.0
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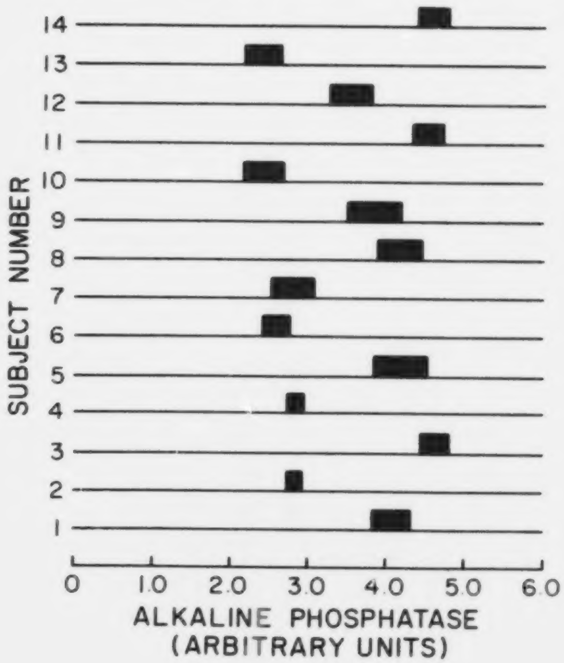
DECEMBER 1975

Figure 9



RANGE OF ACTIVITY VALUES OF ALKALINE PHOSPHATASE IN SERA OF FOURTEEN HEALTHY SUBJECTS FOLLOWED OVER TEN DAYS

Figure 10

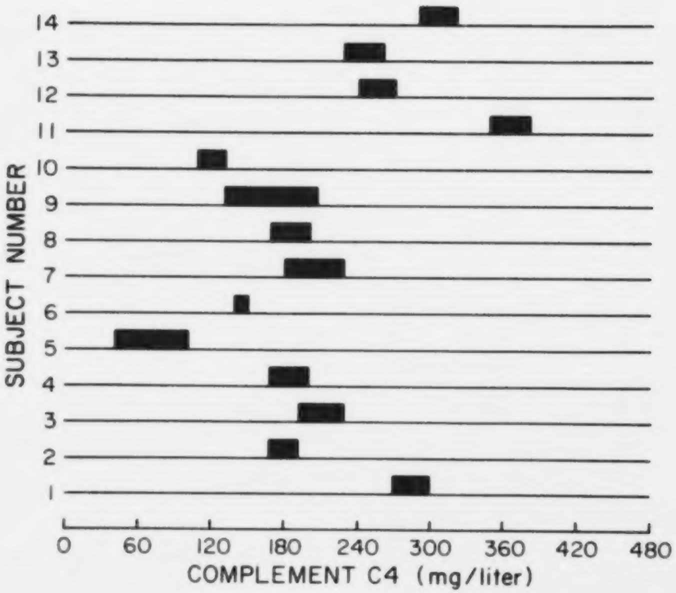


Figure 11

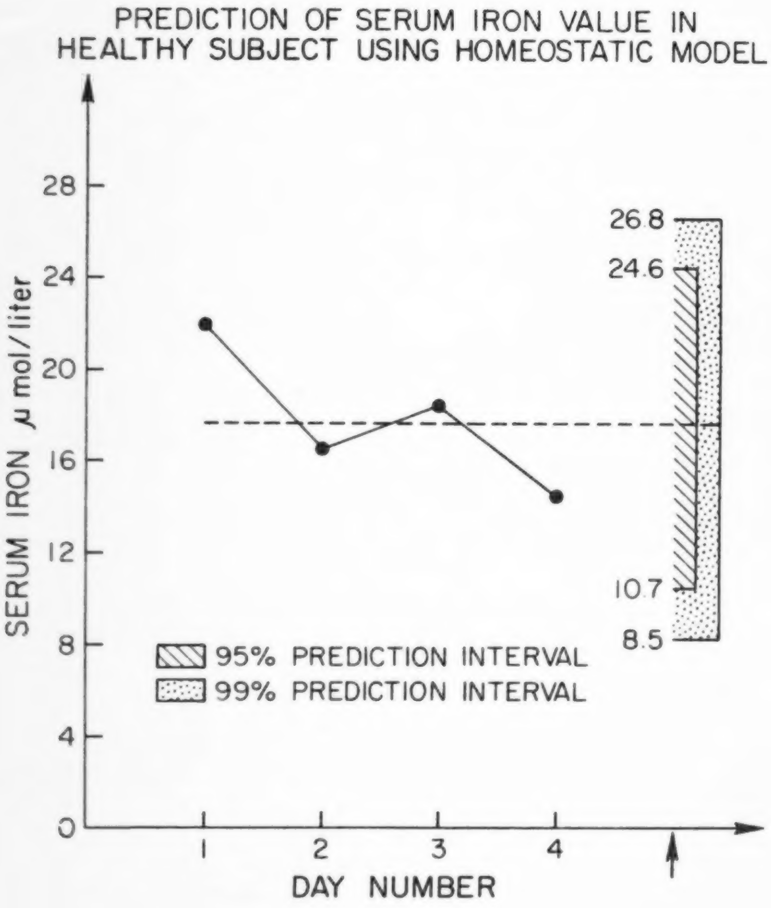

PREDICTION OF SERUM IRON VALUE IN HEALTHY SUBJECT USING HOMEOSTATIC MODEL
SERUM IRON µ mol/liter
0
4
8
12
16
20
24
28
26.8
24.6
10.7
8.5
95% PREDICTION INTERVAL
99% PREDICTION INTERVAL
1
2
3
4
DAY NUMBER

Figure 12

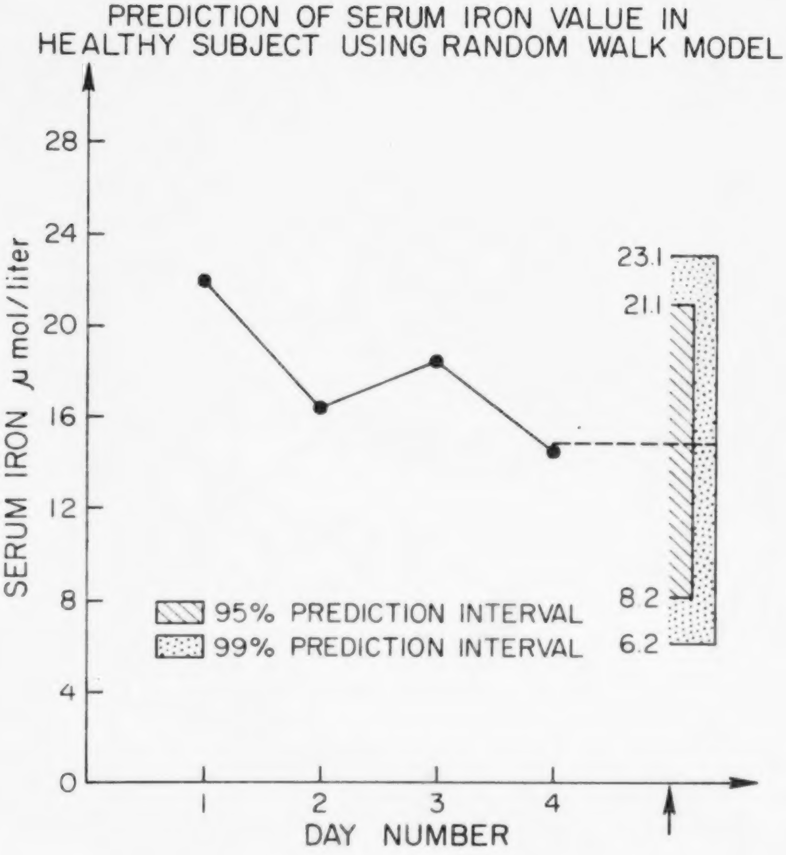

PREDICTION OF SERUM IRON VALUE IN HEALTHY SUBJECT USING RANDOM WALK MODEL
SERUM IRON µ mol/liter
0
4
8
12
16
20
24
28
1
2
3
4
DAY NUMBER
23.1
21.1
8.2
6.2
95% PREDICTION INTERVAL
99% PREDICTION INTERVAL

Figure 13

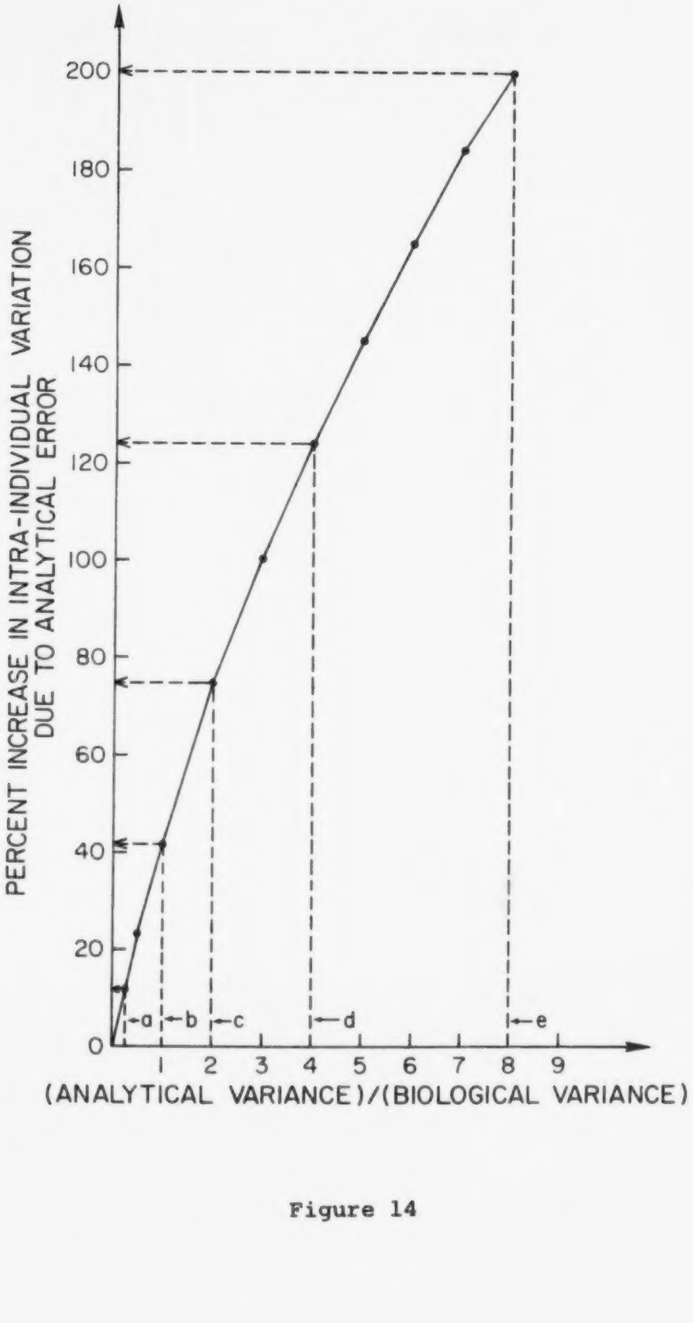

PERCENT INCREASE IN INTRA-INDIVIDUAL VARIATION DUE TO ANALYTICAL ERROR
200
180
160
140
120
100
80
60
40
20
0
a
b
c
d
e
1
2
3
4
5
6
7
8
9
(ANALYTICAL VARIANCE)/(BIOLOGICAL VARIANCE)

Figure 14

Discussion

DR. BROMBERG: Apparently, there are many sources of what in the first approach we might consider as noise. However, part of this noise apparently is not noise. It is a response to other variables that are not adequately controlled. So, in experiments, the researcher tries to look at some of these variables. For example, muscular exercise unfortunately has some prolonged effect on certain enzymes.

Other sources of variability apparently remain completely undiagnosed, and we call them noise. Evidently, there are two kinds of noise, some of which we may understand and try to control in our experiments, and others that are beyond us, which we have to live with.

The worse the total noise, the more limited we are in looking for subtle or small effects on signals. How do we deal with that problem? How do people like Dr. Horvath, Dr. Frank, and Dr. Battigelli--all members of the panel who are, in fact, very much concerned with making measurements in man and picking up relatively small effects--deal with this problem in a practical sense?

In addition, how small are the effects that we ought to look for? Is there some limit we ought to impose on ourselves and not attempt to look for effects beyond that limit? The experimental situation is too complex for us to eliminate a certain residual level of uncertainty. Perhaps we ought to look only for fairly gross effects.

DR. PENGELLY: I don't know whether we were ahead of the clinical chemists in recognizing this problem of unidentifiable noise, but when we designed protocols for the ozone experiments performed in the late 1960's, it was clear to us that we could not use a population standard for what we would expect. We did not pick a population standard for FEV_1* and then compare a response of an individual.

It was clear that we had to peform what we called sham experiments, in which we allowed for whatever variable that was going to occur. We changed only one variable in the experiment, the exposure to ozone. Then, we repeated the experiment in exactly the same way over exactly the same time period with exactly the same individual and compared the two experiments.

I think this approach has long been the traditional approach to exposures of human subjects to environmental contaminants of this type. Moreover, I think Dr. Frank was very impressed with the results of the controlled experiments conducted at the facility here--how the individual variability is quite small and how well individuals have been characterized. I think that the lesson of the significance of intra-subject variability has been learned in this area.

DR. BROMBERG: But you have not controlled for the effect of time in your procedure. You did an experiment on day one, and you made some assumptions as to how long you had to wait to do a valid experiment, a sham experiment, and then you conducted that sham experiment several days of weeks later. You were still left with some potential for variability.

DR. PENGELLY: I think the important point was to compare the individual against himself.

DR. HORVATH: In one sense, I disagree with you, Dr. Pengelly. In the first place, I believe that we all have an idea of how to handle intra-subject variability, but I think Dr. Statland's observations indicate very clearly that this is all a figment of our imaginations. It leads us into an uncomfortable situation of evaluating the effects of anything on a human organism.

One of the points I made in my presentation was that the investigator has to prepare the subject. Dr. Statland has emphasized this point. There are three variables that we have not considered: first, the effects of changes in posture, which can result in a 16-20% change in plasma volume; second, the change in biorhythm, which we have ignored to some degree; and third, the most important factor--what happens to an individual on day A and how long does he have before he fully recovers? I repeat again the statement I made, because I think most people have not looked at all the literature in this field, and I am sorry to say that I did not know about your work either.

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*forced expired volume in one second

It is certainly obvious that it takes many days to recover from any kind of strenous activity. Recall Dr. Statland's data. Out of 10 marathon runners, only two were able to complete a short, 5 mile race 5 days after they had run a 2-1/2 hour marathon race. Moreover, the two subjects who completed the short race were unable to run it at the same speed they had run the 26-mile marathon 5 days earlier. It took almost 7 days for some of the blood parameters (hematocrit, for example) to return to normal. It appears to me that some of the effects we are looking at are very definitely hidden by our failure to know exactly what has happened to the subject.

I am just as guilty as anybody else because I accepted the same premises you did, Dr. Pengelly. But I am convinced now, after what we have been doing the last 2 years in this area, that we have made horrible mistakes. We have got to use an entirely different approach in our testing.

DR. BROMBERG: Dr. Horvath, let me ask you a question. Suppose I do an experiment where I compare vital capacity measured on day two after exposure to gas "x," to the vital capacity measured on day two following a double-blind exposure to scrubbed air. I find the exposure to gas "x" in four out of four subjects has apparently resulted in a reduction in the vital capacity of 5%, plus or minus 1%. Every single subject went down, but one went down 4%; another, 5%; another, 6%. Now, have I found anything?

DR. HORVATH: Of course you have found something, but what do your findings mean? I think everyone has done about the same sort of thing. However, the point is do your findings represent anything in terms of what has happened to the subject? For example, one of the things we did with ozone was to show very clearly that the greater effect is observed immediately after the individual has finished exercising. If you waited half an hour or 15 minutes, the effect is less: that is, the decrement is smaller.

I feel very strongly that we have missed the boat with regard to our approach. We have missed it because we still work on the basis of old-fashioned statistics; namely, we use "T" test for evaluating everything, and that is not a critical way to evaluate the test results.

I think we are in this same position right now. I just want to say that Dr. Statland made a very nice presentation because he brought out three important testing considerations: time, day-to-day position of the subject, and the effects of the studies done prior to the time the individual was used as a subject.

DR. BROMBERG: You feel not that we have missed the boat, but that we have over-interpreted the boat?

DR. HORVATH: Well, that is missing the boat.

DR. BATTIGELLI: I would like to mention that Theodore Hatch said some 10 or 12 years ago when he stated that our ability to measure and to identify factors of possible injury far exceeds our ability to interpret the meaning of our measurements. He stated that at times we may vastly exceed our ability to interpret effectively what we can observe and quantify quite carefully.

But indeed, I think the reply to the question we are discussing is what Dr. Statland and Dr. Horvath have presented to us, and what Dr. Frank and Dr. Pengelly have stressed--the proper design of an experiment. By proper design of experiments, I mean segregating all the significant variables (whether irrelevant or important) that may affect the detection or the observation of the effect. Once we accomplish that, we can proceed to the next step, which is to interpret change and/or effect.

But in recent times, and this is probably what Dr. Horvath alluded to, all too often we have made interpretations based on crude designs, mixing into that process various factors so that the significance in the causation of the effect observed is lost or equivocated.

DR. BROMBERG: What I think you are saying is that we ought to design our experiments better so that expert statisticians can help us obtain the absolute maximum from our experiments with the minimum chance of mistake.

I would like to look at this issue a little bit differently. I would like to postulate that we have found a 5% change in some variable that may be of interest. But suppose we had a system of electrical resistors arranged in series, with a total resistance being the sum of all of the resistors. We tamper with one of these resistors, causing its resistance to change 200%. Yet, when we look at the overall resistance of the circuit we see only a small change. It turns out to be a definite change, but a very small one. And we wonder--what does this change mean? If we only focus on the pertinent part of the system, we might then see that we had indeed uncovered a very, very big change.

If I am right, this illustrates the importance of focusing on mechanisms; of trying to understand in detail what is happening, rather than being satisfied with an overall, very small effect and remaining uncertain. Does the response really mean anything? Is it biologically meaningful? Is it clinically meaningful, or is it only a trap? Is it due to poor design of the experiment?

DR. BATTIGELLI: Granted, but don't you find that Dr. Statland's approach is exactly the right way to identify a mechanism? In other words, the statistician is not the only crucial person that can provide us with an adequate design. It is the epidemiological design that probably overrides or is as important as that factor or design that satisfied only medical adequacy.

DR. HORVATH: I think it might be appropriate to have on the record that we are going through our usual 10- or 20-year cycle in research. I would like to point out that in 1966, the New York Academy of Science published an extraordinary review of papers on human variability. I think it would be to our advantage to read those papers again. I think we have forgotten what we intend to do and now we are back on that cycle of remembering again, which is nice to know that it takes ten years to do.

DR. STACY: I would like to inject a note of heresy. Any physiological scientist who has been around for very long knows that there are many factors that comprise the results of any single measurement. If a researcher knows that a factor is going to influence his measurement, he controls that factor. Eventually, though, you have controlled for all the factors that you know about, and you are left with a stochastic residue with which you must live.

But having controlled everything that you know about, you proceed with these experiments and use what statistics you have to get results and draw conclusions from the experiment. I think we are worrying too much about the fact that there are a lot of variables. Of course there are; we know that, so we design around them as much as we can. And what we can not design around, we treat exactly as we do in measuring average evoked responses. We know that there is a lot of noise, thus we take enough measurements to average out the noise.

DR. HORVATH: But my point is that we do control all the variables we remember, but we do not remember all the variables we should.

DR. STACY: That is true.

DR. KNELSON: We might open up just one other area of discussion briefly, and that is the way all of us are used to handling the double-blind, randomized, crossover design where each individual is his own control. It has become almost a cliche in experimental design, but I think there is another aspect that we are missing, which we are beginning to examine. When we study 30 subjects under a set of environmental conditions (in this case, clean conditions), and if we have properly followed all the criteria Dr. Otto talked about in selecting these subjects, there is no reason to believe that our test subjects are not as representative of the universe that we are trying to estimate as the next set of 30 that we select, using the same criteria.

We we study the next 30 subjects under the experimental conditions, we do not have the compounding variable of a person serving as his own control, but during that time he has experienced a set of environmental conditions that may have changed his control. So, using multivariant statistics where 30 subjects serve as a characterization of the universe that we are trying to estimate some parameter of, and then taking another 30 and using them in only the experimental situation, you do not go back to the old "T" test.

I think we get some statistical follow-up at times there. We may also be getting a better representation of the population. In clinical medicine, frequently the population of concern is a single individual. That individual is the universe of concern. We are concerned about 200 million citizens of the United States.

DR. HIER: I would like to expand on that, Dr. Knelson. The idea of using an independent control group can be important in that when you start, the subject who undergoes a "control" experiment is permanently altered; consequently, you no longer have a fair comparison if you use that subject as an experimental subject, too.

You can counterbalance that by giving him an experimental control, but that takes a long time. You can have your cake and eat it too, in a way, by giving each subject a baseline run without experimental intervention, giving one group of subjects two baseline runs and the other group of subjects a baseline and experimental run. The baseline run that is given to one group of subjects, which is the next experimental line, serves as a control for individual differences.

Then you can subtract or use an analysis of covariance for each individual difference, for each individual's characteristics. That way you do not have to worry about the permanent alterations that occur every time you do something to a person.

DR. STATLAND: You are right. You are about ten years ahead of clinical chemistry. But the reason why you are is that the concept of preventive medicine has only come about recently within clinical medicine. Basically, we have been very therapeutic in nature. We have looked at the disease after the cause. I think medicine is changing in general, not just clinical chemistry.

The second reason we clinical chemists are now looking at the same issues as you is because our analytical procedures are now so much more precise and so much more accurate. We can do a glucose test today much more accurately than we could in the past. Therefore, the question is: With this extra analytical precision and accuracy, what are the other issues that we want to deal with, that we want to consider and control?

Just a few comments about points that have been mentioned before. One of the concerns when you compare two groups of 30 individuals is trying to define analytical variations. And, of course, that occurs within the subject as well.

As you become more proficient in conducting experiments, you also may change certain things, for example, the number of baselines to have on the subject or the type of biological time series model that one must adopt.

Statement

L. David Pengelly, Ph.D., P.Eng.
McMaster University
Hamilton, Ontario

I am approaching this topic, "Special Considerations and Approaches," wearing three hats. My first hat is an electrical engineer. As an instrumentation engineer, which I was for many years with David Bates, I am concerned about the precision of all environmental and biological measurements. We had quite a lot of good discussion about this, and I think we could perhaps still have a little more.

My second perspective is as a physiologist. I am concerned about the need for a broad testing approach, and in fact, we have already touched on some of the effects of biological variables. One variable that has not been mentioned, which I think is very important, is the age of the subjects.

Racial origin, for example, may be a very important factor in test responses. The hormonal effects, such as the estrus cycle in females, is obviously a factor that should be taken into account. These variables have already been referred to. The question of whether you are measuring the right thing should also be included in the broad approach. One always has the suspicion that he may have overlooked a sensitive factor that should have been measured.

Last of all, right up there on top, is my third hat--as an air pollution health effects scientist. I feel strongly that early studies on the synergistic effects of pollutant gases and so-called inert

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aerosols will be necessary to enhance the credibility of the chamber studies that we are conducting.

Perhaps I might take issue with Dr. Frank on this point. Obviously, one should not begin this type of study with a "Let's see what happens" attitude. I think there is ample evidence that the aerosol particle is a very special vehicle for conveying pollutants to nasty places.

I would now like to elaborate on these points. The first issue concerns the precision of measurements. In the early days, many of us used simple homemade chambers made of plastic and a few bits of angle iron. In Figure 1 note the high-volume sampler we used to measure suspended particulates, and that the subject is sitting at a desk. That is the sort of elementary approach we used.

Figure 2 shows our pulmonary data acquisition system. It is a very simple acquisition system, but I think it is aesthetically more pleasing than the ones that you have here. It is capable of a certain amount of independent programming. I included these figures for historical interest, and to show you that we use a very simple, inexpensive approach.

We cannot compete with the EPA in terms of throughput or in the detail of the meticulous studies you are capable of here at the Health Effects Research Laboratory. Consequently, I think that places a special responsibility on you for giving us the data on the studies you have performed. The tools that you are using--computer data acquisition on pulmonary function performed--are by far sharper tools than the ones we have been able to use in the past.

The fact that analytical variability has now been reduced affords us the opportunity to produce unique information on the variability of baseline levels on which many pulmonary functions are based. The problem of variability and precision of measurements is one that you are in a very good position to attack and document.

I suggest that it would be wise to document and analyze these baseline data formally for the rest of us so that we can have the advantage of your experience. In addition, I think you should very carefully establish the type of measurement protocol that you plan to follow. If you use a protocol that is not generally accepted, we need explanations as to why you think it is better.

The second point I should like to examine concerns the choice of subjects. There are a number of factors that play an important role in subject selection. When choosing subjects, one must be concerned about the sources of known variability. The age of subjects

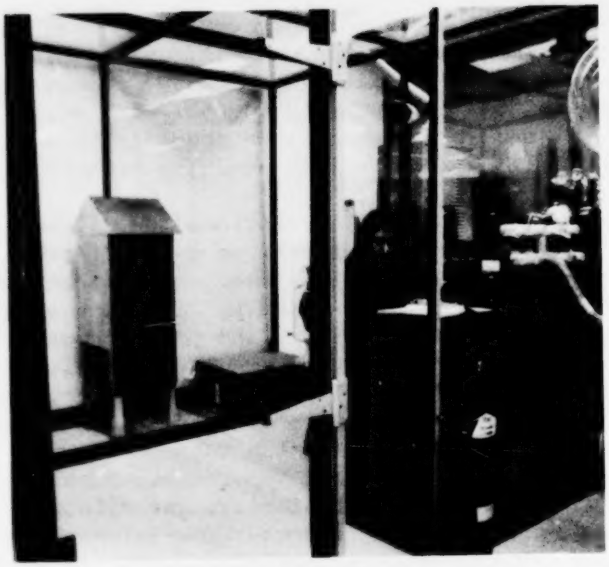

Figure 1

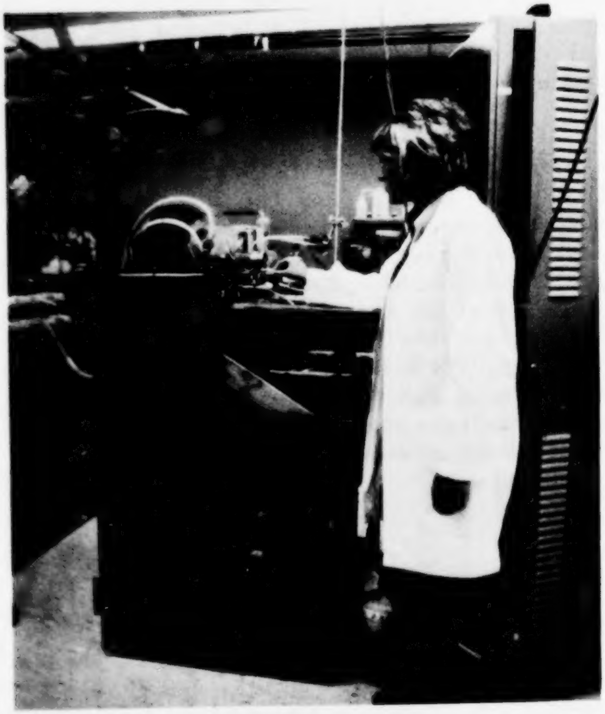

Figure 2

is one example. I am not completely convinced that it is sufficient to examine the response of young, normal, white, male subjects which, if one examines the literature today, represent by far the greatest number of human exposures to pollutant gases. I think it is very important that researchers be prepared to study a wide age spectrum--probably as wide as from seven to seventy years.

Other factors of variability include the difference between smokers and non-smokers; the effects of cyclic, natural, and therapeutic hormones; and, perhaps even as has been suggested, the influence of diet. The studies done by Jack Hackney suggest that factors such as place of residence, and polluted or non-polluted environment, may very well play a role in variability.* For example, using gas for home cooking might be a very important determinant as to how a person responds to oxides of nitrogen. As a respiratory physiologist, I also suggest that the kind of pulmonary function test chosen is important. I think that the current use of the single-breath foreign gas dilution, the so-called "closing volume test," and the flow-volume curves done with air and helium-oxygen mixtures, could be useful adjuncts to a protocol.

I am sure you have agonized over what sort of test would be the most useful and sensitive. I think the evaluation of changes in non-specific bronchial reactivity is also likely to be useful, but again, there is a limit on what you can inflict on test subjects.

My last point is in support of what Dr. Bromberg has suggested. I, too, would like to make a plea for the study of mechanisms. I suggest that resources such as people who are able to interpret mechanisms would be a very useful adjunct to the operation of the Health Effects Research Laboratory. I think it is not enough to say that a given level of a given substance does not produce a specific effect of a certain class. If we are to gain insight into the lung's defenses, into other disease entities, if we are to get more output from these kinds of studies than just that output directed towards standards settings, then we have to be in a position to shed light on the mechanisms.

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*Hackney, J.D., W.S. Linn, S.K. Karusa, R.D. Buckley, D.C. Law, D.V. Bates, M. Hazucha, L.D. Pengelly, and F. Silverman: Effects of ozone exposure in Canadians vs. southern Californians: Evidence for Adaptation. Arch. Env. Health 32 (3): 110-116, 1977.

Discussion

DR. OTTO: Obviously, the lungs are one of the primary sites through which air pollutants are ingested, but it seems to me that we have inordinately emphasized pulmonary function. I think the panel should discuss other organs that might be targets of air pollution effects.

DR. BROMBERG: It is true that carbon monoxide is the noxious gas that is most often considered to affect other systems, and the lung is the portal of entry for carbon monoxide. Work with other gases has focused primarily on pulmonary effects.

On the other hand, for ozone there is evidence that red cells are affected. In a more hypothetical vein, immunocytes present in the bronchus, which is associated with lymphoid tissue just underneath the epithelium, may be affected. These immunocytes are local, but they do communicate with the body's overall immune system.

Other gases may cause changes in capillary endothelial cell function, which would result in more widespread changes in the circulation. These effects are a bit more remote and probably are not as attractive as topics for study as the pulmonary effects.

The clinical side of the coin is that people die of lung disease or suffer from chronic pulmonary symptoms: consequently, lung function has received more attention than other, less directly affected sites in the body. I would like to know what other people think.

DR. KNELSON: We should make it explicit in this discussion that we are addressing only a few facets of a large problem. Much of what we have talked about touches only the periphery of the air pollution testing program currently underway at the Health Effects Research Laboratory. In our laboratory, we invest as many resources in the study of in vitro cellular toxicity testing as we do in pulmonary function testing. For several years, we have had a relatively ambitious psychophysiology neurobehavioral program. We collect venous blood cells from exposed subjects and study the immune competence in these cells in vitro. We also conduct rather aggressive metabolic tests on these subjects.

DR. HAZUCHA: I would like to comment on Dr. Otto's remark. It is true that we are concerned with pulmonary function because it is a primary target, and I have no doubt that different pollutants will affect the systems within the body. But if we compromise in measuring pulmonary functions, we will have to be prepared to compromise in studying other systems.

When I measure vital capacity, I do not care if the subject drinks a glass of water or eats a sausage in the morning. If, however, I want to measure some level of enzymes, I certainly will be concerned with what the subject has eaten. The more sophisticated test I use, the more I have to be concerned with factors such as the subject's posture or the time of day, or any of those factors mentioned by Dr. Statland earlier.

DR. KNELSON: I would like to amplify what Dr. Hazucha is saying. We have already designed experiments that are impossible to conduct. The interests of the psychophysiologist, the interests of the clinical chemist, the interests of the cardiologist and the pulmonary physiologist are converging on a group of subjects that allows us to write a protocol we can never implement. As a result, we sit back and say, "Well, which variables can we afford to measure at this stage; which ones are we going to have to put off for the next experiment?"

DR. BENIGNUS: I have heard several of you comment that theoretical work, backup work on the mechanisms of the effects we observe, is important and necessary. Because it contributes to the body of knowledge about physiology, such work is not only necessary from the academic point of view, but also from the point of view of credibility.

I do not, as a scientist, have much faith in results that show only a decrement in some kind of performance--for example, the dose response curve. As a scientist, I would have much more faith in results that explain to me the mechanisms that produce the effects. Work of this type is not just a matter of contributing to the academic pool; it is a matter of gaining credibility in the scientific community.

DR. HAAK: To amplify that, Dr. Pengelly mentioned that perhaps our activities are directed toward setting standards. I believe that when our recommendations for air quality standards, which may be based on the 5% decrement in pulmonary function that Dr. Bromberg mentioned, are tested in court, the judges will require some mechanistic formula to interpret how many millions of dollars our recommendations will cost. Scientists from industry will argue that a 5% decrement does not warrant the expense of millions of dollars. Other scientists will be asked to explain what impact a 5% decrement will have on public health.

As long as the mechanism is not clear, the court and the judges will be unwilling to make a multi-million dollar decision. The issue will be a stalemate. The scientists will be sent back to the laboratory to do more research to support their recommendation of a particular standard. And that research will have to be based on the expected mechanism of the pollutant at issue.

DR. OTTO: Allow me to cite one example that puts this issue into perspective. We have not said very much about our neurobehavioral research. In fact, the results of our studies, which in some cases reveal positive findings, have had virtually no impact on standard setting in this country, even though we have been collecting data for five years.

One of the reasons that we have not had any impact is that when we measure brain waves, for example, and we notice an increase in a given component, we do not know what the underlying mechanism is for the change in that component. Therefore, our friends in Washington, who have to evaluate this data, say, "So what? You showed a change in the brain wave function; I can pick up my cup of tea and joggle it around and show changes there, too, but what is the functional significance? Until you can tell me the mechanism and what its functional significance is, I really do not know how to evaluate your data." The mechanisms must be described before we can really interpret the effects that we observe.

DR. BROMBERG: I do not know whether I know David Bates' point of view well enough to speak for him, but my impression is that he would say, "If you have demonstrated a reproducible effect, that effect speaks for itself. The burden is on those who would deny the significance of that effect to prove that it has no significance. To those individuals, I simply say, 'Well, I saw something happen, and if you cannot disprove that it happened, then I have proved my case.'"

What about that point of view? Do you deal with this at all, Dr. Frank, in thinking about what it is you want to measure?

DR. FRANK: Yes, I do. I have stated that dose response relationships have considerable impact in this field. Let's face it--they do. Ultimately one of the issues that we should address--and this is kind of circular--is that basic research, dose response relationships, animal toxicology and epidemiology all feed into one another. To the extent that any one of these elements is isolated, you can forget about it, if it cannot be drawn into the entire picture. If animal toxicology and clinical research do not inform and influence the design of epidemiologic studies, then we are spinning wheels. I think we all agree on that.

My bias is toward studies of mechanisms. This is what fascinates me. For example, we are in the process of trying to find a basis for what may be the vulnerability of certain individuals in the population to sulfuric acid. There is a good analytical chemical basis for this notion, and I think it could be tested and that such a test would not only be informative, but also great fun.

As scientists we ought to anticipate being confronted with the problem of how to relate our observations to some remote entity, such as lung disease, or even "public health." We should be prepared to say, "I have made an observation and I do not understand it, but I think it has the following implications." Then we should begin to test the hunch.

We should not say, "Here's my observation; it is an effect." Implicit in that statement is the notion that all effects are bad. I do not think they are. I have seen some data on dose response relationships to ozone obtained from an extremely good laboratory. The data were presented as evidence that there was an adverse effect, beginning at about 0.3 ppm of ozone. My reaction to the data was that it was reassuring that there was virtually no adverse effect in the subject when he was breathing at rest. In my judgment, the deviation from zero was almost trivial; it was within the variance of the measurement in the population.

DR. BROMBERG: It is hard to know what to do with small changes. One man's artifact is another man's Nobel Prize. A small change may be a very significant piece of information if we only knew how to isolate it, to focus on it, and to amplify it and understand it.

DR. FRANK: I couldn't agree more.

DR. BROMBERG: On the other hand, a small change may really be nothing.

DR. FRANK: Again, I couldn't agree more. What is an apparent certitude today may change radically in its implications tomorrow. We do not have final truth on anything, and there is always the danger of over-interpreting data. But we do end up with a lot of curiosities, and it seems to me that they get in our way. The curiosities exist, but we avoid exercising judgment about them.

It would be ideal if we could eliminate all environmental stress, but we are not about to do that. What we have to try to do is exercise a certain amount of judgment about how much is tolerable.

DR. HORVATH: I would like to make one facetious comment and one serious comment. The facetious comment has to do with the "beneficial effects" of ozone exposure. My reaction to that is as follows: one of the things that we discovered was that the maximum aerobic capacity--in other words, the capacity of a man to work at a sustained level--seems to be reduced because of ozone exposure. I say that may be beneficial because it may prevent all of us from becoming over-worked; so, if we are exposed to ozone, we may actually be benefitted by it.

My serious comment concerns Dr. Pengelly's important suggestion; namely, that we are ignoring the effects of age. The only studies I know of that contain any data on age were the studies we did with carbon monoxide. We looked at young Caucasian males, middle-aged Caucasian males, and we looked at smokers and non-smokers, depending on whether they had smoked at least one pack of cigarettes a day for a couple of years or for 16 to 17 years. We noticed differences among these groups.

But that is the only study on age groups that I know of. We have ignored the effects of age for all the other pollutants, and I feel strongly that the age factor must be taken into account because we do know there are obvious changes that occur in individuals as a consequence of age and as a consequence of sex.

Age and sex have to be involved in any consideration we give to what happens to the population. After all, 10.9% of the population in the United States is over the age of 60. That is a huge percentage of our population. The point that Dr. Pengelly did not bring up, however, which annoyed me considerably, especially since in my laboratory we have some very strong people who are of the opposite sex, was the influence of sex hormones. He hinted a little bit, but I think we have to consider the striking differences between males and females. We are completely ignoring 53% of our population. Every time I ask someone if they support studies on females, they look at me and say, "Well, females are females." They are, indeed, and from the standpoint of being good subjects, they are much more attractive than males.

We are also ignoring the elderly. When you talk about pollutant effects on humans, what groups are concerned? Who dies? It is not the young Caucasian male and female. It is the old Caucasian male and female, and we have paid no attention to them. This is one of the real difficulties that I find with all of the experimental work that is being conducted on air pollutants. We will have wasted a great deal of money if someone does not start to support studies involving females and the elderly. The cost benefit problem is of no importance if you relate it only to young Caucasian males.

The factor of race is another problem that we have ignored. Studies suggest that the responses of other races to environmental stresses are different from the responses of Caucasians. We must seriously consider the factors of age, sex, and race. We must move quickly to incorporate people from these groups into our studies, even though it is not easy to recruit subjects from the population at large.

My feeling is that no human organism can survive if he isn't under some environmental stress, and I do not think we can remove stresses from the organism. I am not sure that we can benefit by studying ozone or dioxides as stresses, but I do think that we have to have a certain degree of stress.

Before we decide whether or not these minor changes that we have been recording are bad for us, I think we must ask ourselves, "How much do we need of this stress in order to survive?"

Statement

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I shall briefly attempt to offer some encouragement to consider human experimentation as a legally, socially, academically, and medically acceptable endeavor.

Experiment is such a common event in life--certainly it is common in many professional habits and commitments--that maybe something is lost by using the term. Some of you may remember the lovely poem by Emily Dickinson that ends something like this: "Experiment to me is everyone I meet."

Some of you may remember the well-known British cardiologist who stated that any time a physician embarks on a treatment of a patient, he is conducting a clinical experiment. Justice Holmes remarked that "All life is an experiment; the best test of truth is the power of the thought to get itself accepted in the competition of the market."

"A test, a trial, a tentative procedure" is the dictionary definition of experiment. The thought process that we have accepted in embarking on experimental work will be exemplified by discussing our experience in byssinosis.* I shall from the outset define that we are not testing the entire pathogenesis of byssinosis, but only a very small aspect of it--the acute ventilatory response to calibrated clouds of cotton dust.

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*Byssinosis is a form of pneumoconiosis due to the inhalation of cotton dust.

Whenever we deal with cotton dust, we face a complex, heterogeneous mixture of particles that may be derived from contaminating dirt or from various parts of the cotton plant--the fibers, the shell or pericarp, the bracts (small leaf-life appendages at the base), the stem, and the leaves.

Exposure to cotton dust is associated with the development of a syndrome we call byssinosis. This syndrome is an airways response, a sort of asthma, which is associated with well defined symptoms that have a characteristic cyclic expression, at least at the beginning of the natural history of the disease.

The subjective syndrome is part of a phenomenon that may be objectively identified as a respiratory decrement, a respiratory loss following exposure to dust, well described by the spirogram. We also recognize that not all of the individuals exposed to cotton dust come down with a significant response, and that the proportion of those affected increases in proportion to the intensity of the exposure. It has also been ascertained that individuals not used to the occupational exposure may, on exposure to sustained concentration of dust, exhibit the symptoms, as well as the signs of the cotton dust effect.

In any area of knowledge, there are certain aspects that are out of focus, incomplete, erased, or totally missing. One of the aspects that we thought interesting was to verify how specific was the acute ventilatory response related to other conditions that we distinguish from byssinosis. What is the dose-relationship of the specific response, and the specific agents causing these responses in patients, volunteering as subjects, or in normal healthy individuals who are free of disease and unexposed.

The primary justification for collecting information on dose-response relationships is that such information is helpful in formulating appropriate medical management procedures, including removal from exposure, reassignment, relocation, retirement. Hence, experimental exposure may assist in defining guidelines for this type of decision. There is more to it.

We considered several questions as clinically significant to our study. First, is there a minimal concentration and/or duration of exposure that is effective in identifying the specific, segregated ventilatory response, whatever the relationship of this may be to the whole syndrome? Second, are there any specific characteristics of reactivity (such as symptoms or objective ventilatory parameters) that can be defined and perhaps related to the pathological background of each subject? Third, can these definitions of reactivity characteristics be used to formulate pathogenetic considerations?

The fourth question is, are there specific components or characteristics of the exposure, the nature of the dust, that can be identified as most injurious and therefore necessary to the understanding of the natural history and the pathogenesis of the disease?

In designing and executing the experiments, considerations of safety are quite straightforward. Our continuous monitoring program is maintained by assaying dust level continuously and by having a physician exposed to the same conditions as the subjects, in the exposure room.

The nature of the response, at this concentration, is limited and invariably reversible. We must recognize that the true experimental value to these activities is simply that we duplicate what happens in the real world within total uniformity and continuous control.

In doing so, we find justification in trying to remove the bad connotation from the word "experiment." This term conjures visions of vivisection, which, of course, excites the minds of those who tend to see greater risks than actually are warranted in these circumstances.

I would like to pass on this word of encouragement, quoting from no one less than Jacob Bronowski, who said, "We live surrounded by the apparatus of science, the diesel engine, the experiment, the bottle of aspirins, and the survey of opinion. We are hardly conscious of that, but behind that, we are becoming conscious of a new importance in science. We are coming to understand that science is not a haphazard collection of manufacturing techniques, carried out by laboratory dwellers with acid-yellow fingers and steel-rimmed spectacles and no home life.

Science, we are growing aware, is a method and a force of its own, which has its own means and style, and its own sense of excitement."[2]

One may wish not to call an experiment an experiment; let us call it a justified verification of an hypothesis, but the fact is that that type of endeavor is here to stay. We are bound to conduct experiments, and perhaps a safe beginning is with a restatement, according to what Socrates suggested, "The beginning of wisdom is the definition of your own terms."[3] I suggest this for your own activities.

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Discussion

DR. BROMBERG: Yesterday Dr. Bates said that he thinks certain experiments are best conducted in the environment where the problem actually exists. If, for example, you want to study the long-term effects of sulfur dioxide, perhaps the best place to do so is in the work setting of lead smelters, and not attempt to study the long-term exposures in a chamber.

Perhaps the smaller, better controlled studies that we do in the laboratory should be viewed in this context. As long as we do not exceed the exposure levels that are occurring in, and are accepted by, our industrial society, perhaps we should consider the real environment as a standard of reference for what we should permit ourselves to do or not to do.

DR. CRIDER: If you use the workers in a particular industry as your subjects, you may be omitting a large percentage of people who may be susceptible to a particular agent. Individuals who can survive potentially harmful environments tend to continue to work in them; those who cannot, do not. I think we would have to be careful in conducting the type of studies that you suggest, and in selecting subjects for them.

DR. BROMBERG: I am not saying that one has to go into the field and find individuals and study their responses to controlled laboratory exposures. I am just saying that our society has indicated, for the moment, its willingness to tolerate certain levels of human exposure. By using society's willingness to tolerate exposure as a standard of reference, perhaps the much more careful approach we use in the laboratory is really quite defensible. There may be another perspective from which to view our experiments other than the almost frightening portrayal suggested by moralists, chairmen of human use committees, and doctors of jurisprudence.

Dr. Battigelli did not really discuss in detail any of the work that he has done, but many of his subjects are not people who are occupationally exposed to cotton dust, or who have any history of byssinosis. They are people who have well-defined, chronic obstructive lung diseases of more common varieties, but who are nonetheless willing to be exposed to cotton dust. They are exposed along with the experimenter himself, who sits in the chamber with the subjects and is as close as the touch of a hand.

Very interesting information has been obtained from Dr. Battigelli's studies, and I think in our studies of pollutant gases, for example, that we ought to pay more attention to the possibility of using that difficult-to-control, more worrisome kind of subject, the individual with well-established chronic disease.

DR. BATTIGELLI: Because you conduct experiments within a controlled laboratory setting, you can easily defend your activities by demonstrating that the subjects you expose are immensely safer than other subjects who are exposed to the same variable in a less controlled situation.

With regard to the variety and characteristics of exposure subjects, one should include the ill and impaired. There is no question that the impaired individual is quite often, if not always, a very sensitive responder. I am sure that your protocols have included exposure of individuals with significant disorders because such people are, perhaps, more sensitive to the various factors you wish to study.

DR. PENGELLY: Earlier, someone asked about the meaning of a 5% decrement in vital capacity. Vital capacity is a measurement of pulmonary function, and it is well known that it decreases with age. After growth stops, vital capacity drops approximately 0.5% per year. If one's vital capacity declines 5% over a two-hour period, that is comparable to ten years of aging. Even though the vital capacity may return to its original level, I think this suggests that age is an important factor to consider when we decide what we should measure and how people respond.

It is well known, for example, that cigarette smoking produces a vital capacity decrement that is greater than the normal decrement associated with age. If exposure to some toxic material causes a decrement in excess of the known decrement, I think that is a sufficient argument to say that although this person may still have, functionally, enough vital capacity to get on with life, the fact that he will deteriorate at a more rapid rate than he would otherwise is a significant point.

Knowing the effects of cigarette smoking on pulmonary function, knowing that the cigarette causes 60% of all cancer mortality, how can we justify the question of sensitivity to air pollutants in the face of such an enormous known stress to the lungs?

DR. FRANK: I would like to respond to this, not with respect to cigarette smoking, but with respect to vital capacity. We could be dealing with substances X, Y, and Z--call them pollutants for the moment--and we could administer each of them to a carefully controlled group in which we know the subjects' previous diets and all the factors that may influence their functional response.

To measure vital capacity, we expose the subjects to pollutants X, Y, and Z for 10 minutes. Each person shows a 5% reduction. At this stage, there is no way of weighing the importance of the changes in vital capacity. We are not yet in a position to judge the relative significance of the reductions in vital capacity. So, we expand the experiment; we may also use information obtained from the subjects while seeking answers to other experimental questions. Which of these pollutants is the most important? Are they all equally important, or are none of them important? We may find that if the subject is exposed to agent A for ten minutes on each of three days there will be a constinuous drop in vital capacity; but for agents B and C the subject will revert to control with repeated exposure. Perhaps now we are developing a reasonable hypothesis to suggest that one of these agents is more significant than another.

At the same time, some other researcher develops some epidemiological data that either reinforces or weakens the hypothesis. What I am saying is that it is incumbent on us, as scientists, to continue to test the implications for health, if you will, of the observations we make. We cannot just say that, because an effect has been noted, we have to accept the effect as significant for health.

DR. BROMBERG: I think Dr. Pengelly uses a very convenient calibration scale. He uses those very shallow slopes of function versus age, and extrapolates the data he gets in terms of life expectancy, and says, "Look! This curve crosses the time axis at 100 years, and now you have put this subject, by your little exposure, onto a different curve, which if extrapolated, gives him a life expectancy of only 70 years. You have reduced his life expectancy by 30 years." Is that what you intended to say, Dr. Pengelly?

DR. PENGELLY: No, of course not. What I said was that one has to examine the entire context of the situation, which reinforces what Bob Frank just said. The one little bit of information we get in the laboratory has to be fitted into the other pieces of known information--perhaps in part from animal experimentation and in part from epidemiological studies. The point of view one must have when looking at the response in the lab should be conditioned by the other information at hand.

I certainly did not want to imply that a 10-minute exposure to ozone or some other agent, was going to have some effect on the subject. But, in order to understand what is taking place, one's observations must be made within the context of all the other observations that relate to that variable.

DR. BROMBERG: I think most people would agree with that approach. That does not provide an easy answer to the question of what to do with that 5% decrement. When you were talking, I thought you were saying that the 5% decrement in vital capacity over two hours is the same decrement you would observe after 10 years of aging, and that you can turn around and say to the informed layman, "For you to understand what that decrease in vital capacity means, let me tell you that it is equivalent to 10 years of aging." That is very dramatic, but is it right?

DR. PENGELLY: No, although it does give the layman, in a sense, a framework in which to judge things, but it is not to be interpreted as a value judgment for what happens. For example, if one routinely measured one's weight and noted a weight change of a few pounds over several weeks, such a change is probably not significant. But a consistent change of a few pounds over several days is well known to be significant.

One must keep the scales of age in balance with other information. There are a lot of implications that I have not mentioned; many hidden messages in saying that a change of weight over a few days is important. Many unsaid things come into play because of one's other experience. I think it is important to keep the context in balance.

DR. BATTIGELLI: To extend again what I believe Dr. Frank implied, perhaps a short-term experiment may offer us guidelines and help our progress on long-range experiments. Probably most chronic experiments can be studied better from an epidemiological approach because the study of so-called natural experiments cannot be duplicated in the laboratory by any stretch of the scientific imagination. The interplay between the short-term, bench-type laboratory test and the epidemiological investigation may provide mutual support for both types of experiments and may sharpen attention on important target areas.

DR. BROMBERG: So the lesson, then, for a specially-designed facility like the EPA Human Research Facility here on the campus of the University of North Carolina, is that isolation should be guarded against; the design of the experiment should take into account a wide range of information; and interpretations should be based on an attempt to integrate observations into a coherent picture. The development of this picture is based on animal experiments, on short-term human experiments, on medium-term human experiments, and on epidemiological studies.

I am afraid, though that there will be great difficulties in interpreting the state of the art for a specific regulation that Congress might want to consider. But we must do our best with that problem, and not cave in as scientists to that demand.

DR. HAZUCHA: There are some other implications of acute experiments. It is well known that only ideal systems, when they are stressed, will return to pre-stress conditions. A living organism, to which stress is applied, positively will not revert to pre-stress conditions.

In an acute experiment, the difference between pre-stress and stress conditions may be miniscule. With regard to any of these tests that show a 0.10% decrement, perhaps you cannot state categorically that, over a 70-year life span, there will be a reduction of 7% or seven years of life. But when a subject is exposed many times for many years, the resulting loss of vital capacity will certainly impair the quality of life.

DR. BROMBERG: That all depends on our accepting your original premise, which was that if every event has a permanent effect on the subject, the subject never returns to the pre-stress condition. I am not quite prepared to believe that. For example, we are losing 1% of our red cells every single day. They are disappearing, being eaten up by our reticuloendothelial system. Yet, our red cell mass, over long periods of time, remains quite constant; so it is possible for steady-state mechanisms to maintain constant levels. I think it is possible to undergo some stress and to completely recover from it, and to do so again and again.

I am not sure that either one of us can prove our points, but I think that the assumption you are making, which if we do accept it, would lead us to say, "Well, yes, we have to admit then, that if the same stress is repeated sufficiently often, there will be irreversible, gross, and progressive changes." I am not quite prepared to believe that.

DR. HAZUCHA. It is true that red blood cells are renewed, but the hemopoietic system is stressed, and the hemopoietic system as such will not return to the exact pre-stress condition.

DR. BROMBERG: I am not sure about that.

DR. HAZUCHA: Well, as you said, it is difficult to prove, almost impossible.

DR. BROMBERG: I think you are addressing yourself, in a sense, to your own point of view about the significance of small changes. We have been talking around it, and we have arrived at different ways of looking at the significance of small changes. I think you have developed a way of looking at this which is satisfactory to you, but it still remains a touchy problem. When confronted with a specific circumstance, I suspect various people in this room would come up with a different interpretation of what small changes mean, even after all this discussion.

DR. PENGELLY: I should like to return to Dr. Frank's comments about the importance of observed effects. I am reminded of a discussion I had with a person who supported the development of an airport quite close to a major city. He said that, as he understood it, people living close to airports adapt to airport noise and eventually become accustomed to it. My response to him was yes, there is an adaptive mechanism--it is called deafness, but I do not think deafness is an appropriate adaptation.

Recent studies suggest that people who are not constantly exposed to ozone tend to react more to the gas than people who are regularly exposed to it. The implication of this argument is that individuals exposed to ozone are better off because they do not respond. I argue that the method of adaptation must be considered. Deafness is an adaptation to airport noise, but deafness certainly is not desirable. We must take the factor of adaptation into account; we must make sure it is appropriate.

DR. FRANK: At the risk of being boring or repetitious, I think the new legislation in TOSKA attempts to weigh a risk because weighing a risk is important in deciding what to do about it. I think it is reasonable, too, to say that our judgment of the importance of a risk may be subject to change. We deal always with uncertainty, and what may appear to be, from my point of view, flimsy evidence today, may be quite impressive, overwhelming evidence, if not proof, a month from now.

Consequently, we have to be prepared to change our judgment. But I think, too, that as a society, we are compelled to make judgments because there is no such thing as a benign environment. We have to weigh what it is that we recognize as being most important, and how much of an effort we should make to mitigate harmful stress.

I do not see anything wrong with making judgments. I do not think we should just make observations and put them forth so that finally they become curios. I think if we have any reason to suspect that an observation has an implication, then we, as scientists should pursue our observation and devise experiments designed to test its importance for health.

Another thing that really impresses me is that the biological system is marvelously well constructed to adjust to change. I recognize there is a "price" for all adjustments, but we do manage to adjust.

A hypothesis about to be tested in animals suggests that total dosage may not be important for many of the pollutants we are concerned about. (I am not referring to mercury or lead. They are stored in the body and obviously have cumulative effects.) What is important, however, is the variation in dosage. If an animal is exposed to sulfur dioxide for "X" number of years, the exposure will have no effect if the dosage is consistently low. On the other hand, there will be measurable effects resulting from the same total dosage over the same period of time if the dosage of sulfur dioxide is varied each time the gas is administered. If this hypothesis proves true, it may reveal impressive epidemiological evidence that we can apply to our studies of morbidity and mortality rates.

If humans are exposed to sulfur dioxide more effects will be noticed with a dosage of 10 ppm for one minute than with 1 ppm for 10 minutes. And I suspect you could develop an argument for epidemiologic data to reinforce that as well.

DR. KNELSON: Our two ozone studies demonstrated the importance of variation in dosage very nicely. In both studies, using 0.4 ppm for four hours (which could be expressed as 1.6 ppm of total dose) the effect on lung mechanics was considerably less dramatic than the effect of 0.6 ppm given for one hour, which is less than half of the total dose in the 4 hour exposure to 0.4 ppm ozone.

Our laboratory has also conducted dose-rate experiments, using death in animals as an end point, and we have obtained elegant data showing that ozone does exactly what you have described. These experiments show a continuum of dose-rate response, which is the rate a given dose is administered. We have quantified the dose-rate response, and we have found that short exposures to higher levels of ozone are much more detrimental than long exposures. That does not surprise you, does it, Dr. Bromberg?

DR. BROMBERG: No, but when you are dealing with a potentially noxious agent and with rate-limited disposal mechanisms, and if you increase the rate of delivery to some critical point, you will eventually see a very marked effect. A case in point is the agent potassium chloride. If you make a mistake by injecting 40 milliequivalents of potassium chloride into a patient's vein, in a few minutes the patient dies from cardiac arrest because the circulatory mechanisms that dispose of noxious agents are too slow to cope with that much potassium chloride.

It is not a surprise that if we push hard enough with a concentrated enough dose in a short period of time, we can overcome the effectiveness of the body's disposal mechanisms.

DR. KNELSON: But that is not a consistent tenet in toxicology. You must pay attention to what you are examining. We both know the dose-rate response is significant for toxic substances that the body's repair mechanisms cannot handle.

On the other hand, there are toxic substances that elicit a compensatory response. If you administer a low dose of these substances for a long period of time, the compensatory response will not be invoked, and the overall toxic effect will be greater than if you give the same dose over a short period of time and trigger the compensatory mechanisms.

DR. HAAK: I would just like to pose a final question to this group. If we do not completely understand the mechanism of action, how are we going to get enough concurrence among scientists, ourselves for example, to make a scientifically sound argument before a court to justify the large costs incurred by setting a standard for a given pollutant?

The safe limits for ozone, for example, have been exceeded nearly everywhere. It is going to be a great expense to apply air quality standards to ozone. How are standards for ozone to be defended? Even if we could meet in court, EPA on one side and industry on the other, society will be left without a conclusion.

DR. BROMBERG: We have heard that there is no easy formula. It is clear that various people at this meeting have developed a personal approach to this difficult interface between science and society. They do not pretend that they have the right answer, but at least they have the satisfaction of knowing that they are involved in the issue and have some kind of approach to dealing with it. We do not know the answers to most of the questions that are being posed, and I do not think we are going to know the answers in the very near future. All of us must live with that as best we can.

Appendix

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